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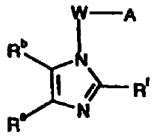
(54) Title: VITRONECTIN RECEPTOR ANTAGONISTS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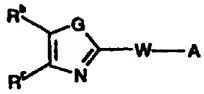
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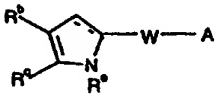
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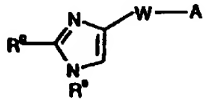
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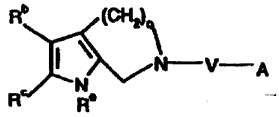
(V)

(57) Abstract

Compounds of formulae (I-V) are disclosed which are vitronectinreceptor antagonists and are useful in the treatment of osteoporosis.

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TITLE

Vitronectin Receptor Antagonists

FIELD OF THE INVENTION

This invention relates to pharmaceutically active compounds which inhibit the vitronectin receptor and are useful for the treatment of inflammation, cancer and cardiovascular disorders, such as atherosclerosis and restenosis, and diseases wherein bone resorption is a factor, such as osteoporosis.

BACKGROUND OF THE INVENTION

Integrins are a superfamily of cell adhesion receptors, which are transmembrane glycoproteins expressed on a variety of cells. These cell surface adhesion receptors include gpIIb /IIIa, the fibrinogen receptor, and $\alpha_v\beta_3$, the vitronectin receptor. The fibrinogen receptor gpIIb /IIIa is expressed on the platelet surface and it mediates platelet aggregation and the formation of a hemostatic clot at the site of a bleeding wound. Philips, *et al., Blood.*, **1988**, *71*, 831. The vitronectin receptor $\alpha_v\beta_3$ is expressed on a number of cells, including endothelial, smooth muscle, osteoclast, and tumor cells, and, thus, it has a variety of functions. The $\alpha_v\beta_3$ receptor expressed on the membrane of osteoclast cells mediates the bone resportion process and contributes to the development of osteoporosis. Ross, *et al., J. Biol. Chem.*, **1987**, *262*, 7703. The $\alpha_v\beta_3$ receptor expressed on human aortic smooth muscle cells stimulates their migration into neointima, which leads to the formation of atherosclerosis and restenosis after angioplasty. Brown, *et al., Cardiovascular Res.*, **1994**, *28*, 1815. Additionally, a recent study has shown that a $\alpha_v\beta_3$ antagonist is able to promote tumor regression by inducing apoptosis of angiogenic blood vessels. Brooks, *et al., Cell*, **1994**, *79*, 1157. Thus, agents that would block the vitronectin receptor would be useful in treating diseases mediated by this receptor, such as osteoporosis, atherosclerosis, restenosis and cancer.

The vitronectin receptor is known to bind to bone matrix proteins, such as osteopontin, bone sialoprotein and thrombospondin, which contain the tri-peptide Arg-Gly-Asp (or RGD) motif. Thus, Horton, *et al.*, *Exp. Cell Res.* **1991**, *195*, 368, disclose that RGD-containing peptides and an anti-vitronectin receptor antibody (23C6) inhibit dentine resorption and cell spreading by osteoclasts. In addition, Sato, *et al.*, *J. Cell Biol.* **1990**, *111*, 1713 disclose that echistatin, a snake venom peptide which contains the RGD sequence, is a potent inhibitor of bone resorption in tissue culture, and inhibits attachment of osteoclasts to bone. Fisher, *et al.*, *Endocrinology* **1993**, *132*, 1411, has further shown that echistatin inhibits bone resorption *in vivo* in the rat. Bertolini *et al.*, *J. Bone Min. Res.*, 6, Sup. 1, S146, 252 have shown that cylco-S,S-N^{α}-acetyl-cysteinyl-N^{α}-methyl-argininyl-glycyl-aspartyl-penicillamine inhibits osteoclast attachment to bone. EP 528 587 and 528 586 report substituted phenyl derivatives which inhibit osteoclast mediated bone resorption.

Alig et al., EP 0 381 033, Hartman, et al., EP 0 540,334, Blackburn, et al., WO 93/08174, Bondinell, et al., WO 93/00095, Blackburn, et al. WO 95/04057, Egbertson, et al, EP 0 478 328, Sugihara, et al. EP 529,858, Porter, et al., EP 0 542 363, and Fisher, et al., EP 0 635 492 disclose certain compounds that are useful for inhibiting the fibrinogen receptor. It has now been discovered that certain appropriately substituted compounds are potent inhibitors of the vitronectin receptor. In particular, it has been discovered that such compounds are more potent inhibitors of the vitronectin receptor than the fibrinogen receptor and such compounds contain a fibrinogen receptor antagonist template.

SUMMARY OF THE INVENTION

This invention comprises compounds of the formula (I)-(V) and (XXI)-(XXII) as described hereinafter, which have pharmacological activity for the inhibition of the vitronection receptor and are useful in the treatment of inflammation, cancer and cardiovascular disorders, such as atherosclerosis and restenosis, and diseases wherein bone resorption is a factor, such as osteoporosis.

This invention is also a pharmaceutical composition comprising a compound according to formula (I)-(V) (XXI)-(XXII)and a pharmaceutically carrier.

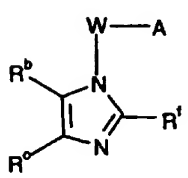
This invention is also a method of treating diseases which are mediated by the vitronectin receptor. In a particular aspect, the compounds of this invention are useful for treating atherosclerosis, restenosis, inflammation, cancer and diseases wherein bone resorption is a factor, such as osteoporosis.

DETAILED DESCRIPTION

This invention comprises novel compounds which are more potent inhibitors of the vitronectin receptor than the fibrinogen receptor. The compounds of the instant invention comprise a fibrinogen receptor antagonist template that is linked to a nitrogen-containing five-membered ring, which is optionally fused to an aromatic six-membered ring. The fibrinogen receptor antagonist template is substituted by an aliphatic substituent which contains an acidic moiety. It is preferred that about fourteen intervening covalent bonds via the shortest intramolecular path will exist between the acidic group of the fibrinogen receptor antagonist template and the nitrogen of the optionally fused five-membered ring.

As used herein, the term "fibrinogen receptor antagonist template" means the core structure of a fibrinogen receptor antagonist, said core being substituted by an acidic group and said core being linked to an organic group substituted with a basic nitrogen moiety. A fibrinogen receptor antagonist is an agent that inhibits the binding of fibrinogen to the platelet-bound fibrinogen receptor GPIIb-IIIa. It is an object of this invention that a fibrinogen receptor antagonist is converted to a vitronectin receptor antagonist by replacing the organic group substituted with a basic nitrogen moiety in a fibrinogen receptor antagonist with an optionally fused nitrogen-containing five-membered ring, preferably an imidazole ring and, most preferably, a benzimidazole ring.

This invention comprises compounds of formula (I)-(V):



(I)

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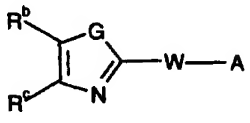

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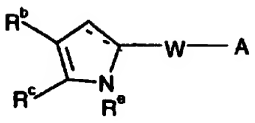

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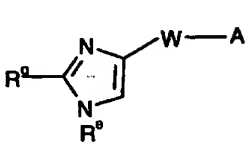

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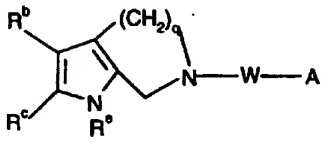


(V)

wherein:

W is - $(CHR^g)_b$-V'- or Ar;

A is a fibrinogen receptor antagonist template;

V' is $CONR^{21}$ or $NR^{21}CO$;

G is NR^e, S or O;

R^g is H, C_{1-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl or Ar- C_{0-6}alkyl;

R^{21} is Het-C_{0-6}alkyl-U'-C_{1-6}alkyl-, C_{3-7}cycloalkyl-C_{0-6}alkyl-U'-C_{1-6}alkyl-, or Ar-C_{0-6}alkyl-U'-C_{1-6}alkyl-;

U' is $CONR^f$ or NR^fCO;

R^f is H, C_{1-6}alkyl or Ar-C_{1-6}alkyl;

R^e is H, C_{1-6}alkyl, Ar-C_{1-6}alkyl, Het-C_{1-6}alkyl, C_{3-7}cycloalkyl-C_{1-6}alkyl, $(CH_2)_qOH$ or $(CH_2)_kCO_2R^g$;

k is 0, 1 or 2;

q is 1 or 2;

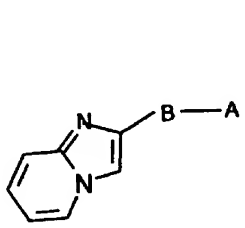
b is 0, 1 or 2;

R^b and R^c are independently selected from H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, or C_{3-6}cycloalkyl-C_{0-6}alkyl, halogen, CF_3, OR^f, $S(O)_kR^f$, COR^f, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, or R^b and R^c are joined together to form a five or six membered aromatic or non-aromatic carbocyclic or heterocyclic ring, optionally substituted by up to three substituents chosen

from halogen, CF_3, C_{1-4}alkyl, OR^f, $S(O)_kR^f$, COR^f, CO_2R^f OH, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, and $CH_2N(R^f)_2$, or methylenedioxy;

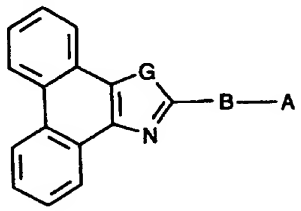
or a pharmaceutically acceptable salt thereof.

This invention also comprises compounds of formula (XXI)-(XXII):



(XXI)

or



(XXII)

wherein:

B is a linking moiety of the form $-(CHR^g)_a-U-(CHR^g)_b-V-$;

A is a fibrinogen receptor antagonist template;

G is NR^e, S or O;

R^g is H, C_{1-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl or Ar- C_{0-6}alkyl;

R^k is R^g, $-C(O)R^g$, or $-C(O)OR^f$;

R^i is is H, C_{1-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl, Ar- C_{0-6}alkyl, Het-C_{0-6}alkyl-U'-C_{1-6}alkyl-, C_{3-7}cycloalkyl-C_{0-6}alkyl-U'-C_{1-6}alkyl-, or Ar-C_{0-6}alkyl-U'-C_{1-6}alkyl- or C_{1-6}alkyl;

R^f is H, C_{1-6}alkyl or Ar-C_{1-6}alkyl;

R^e is H, C_{1-6}alkyl, Ar-C_{1-6}alkyl, Het-C_{1-6}alkyl, C_{3-7}cycloalkyl-C_{1-6}alkyl, $(CH_2)_qOH$ or $(CH_2)_kCO_2R^g$;

U, U' and V independently are absent or CO, CR^g_2, $C(=CR^g_2)$, $S(O)_k$, O, NR^g, CR^gOR^g, $CR^g(OR^k)CR^g_2$, $CR^g_2CR^g(OR^k)$, $C(O)CR^g_2$, $CR^g_2C(O)$, CON R^i N R^i CO OC(O), C(O)O, C(S)O, OC(S), C(S)NR^g, $NR^gC(S)$, $S(O)_2NR^g$, $NR^gS(O)_2$, N=N, NR^gNR^g, $NR^gCR^g_2$, $NR^gCR^g_2$, CR^g_2O, OCR^g_2, C≡C , CR^g=CR^g, Ar or Het;

k is 0, 1 or 2;

q is 1 or 2;

a is 0, 1 or 2;

b is 0, 1 or 2;

R^b and R^c are independently selected from H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, or C_{3-6}cycloalkyl-C_{0-6}alkyl, halogen, CF_3, OR^f, $S(O)_kR^f$, COR^f, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, or R^b and R^c are joined together to form a five or six membered aromatic or non-aromatic carbocyclic or heterocyclic ring, optionally substituted by up to three substituents chosen from halogen, CF_3, C_{1-4}alkyl, OR^f, $S(O)_kR^f$, COR^f, CO_2R^f OH, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, and $CH_2N(R^f)_2$; or methylenedioxy;

or pharmaceutically acceptable salts thereof.

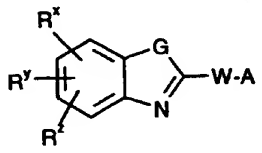
Preferably, U' is $CONR^f$ or NR^fCO.

Also included in this invention are pharmaceutically acceptable addition salts, complexes or prodrugs of the compounds of this invention. Prodrugs are considered to be any covalently bonded carriers which release the active parent drug according to formula (I) *in vivo*. In cases wherein the compounds of this invention may have one or more chiral centers, unless specified, this invention includes each unique nonracemic compound which may be synthesized and resolved by conventional techniques. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, such as  and  , and each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or locked in one form by appropriate substitution with R'.

The compounds of formula (I) - (V) and (XXI) - (XXII) inhibit the binding of vitronectin and other RGD-containing peptides to the vitronectin ($\alpha_v\beta_3$) receptor. Inhibition of the vitronectin receptor on osteoclasts inhibits osteoclastic bone resorption and is useful in the treatment of diseases wherein bone resorption is associated with pathology, such as osteoporosis. Additionally, since the compounds

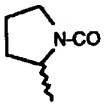
of the instant invention inhibit vitronectin receptors on a number of different types of cells, said compounds would be useful in the treatment of inflammation and cardiovascular diseases, such as atherosclerosis and restenosis, and would be useful as anti-metastatic and antitumor agents.

In a particuar embodiment, the compounds of this invention are of the formula (II), wherein R^b and R^c are joined to form an aromatic ring containing up to two nitrogen atoms. In a preferred embodiment R^b and R^c are joined to form an optionally substituted phenyl ring according to formula (IIa):



(IIa)

wherein G is N-R', S, CH or O.

Suitably W is $-(CHR^g)_aNR^iCO-$ or 

, or, when G is CH, W is $-CH_2CH_2NR^iCO-$ wherein R^i is a methylene group attached to G.

Preferably W is $-CHR^gNR^iCO-$.

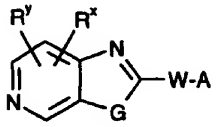
Suitably R^i is H, C_{1-6}alkyl, C_{3-7}cycloalkyl, Ar or C_{1-6}alkyl substituted by one to three groups chosen from halogen, CN, NR^g_2, OR^g, SR^g, CO_2R^g, and $CON(R^g)_2$, Ar, Het or C_{3-7}cycloalkyl. In particular, R^i is H, methyl, butyl, cyanomethyl, carboxymethyl, phenylethyl or benzimidazolylmethyl.

Suitably R^x, R^y and R^z are independently chosen from C_{1-6}alkyl, methoxy, nitro, trifluoromethyl, fluoro, chloro, amino or R^x and R^y are adjacent to one another and are joined to form a methylenedioxy group.

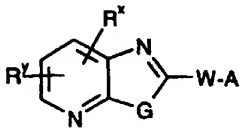
Preferably G is NR^e.

Suitably R^e is H, C_{1-4}alkyl, Ar, Het or C_{1-4}alkyl substituted by Ar or Het. More suitably, R^e is H, methyl or benzimidazolylmethyl.

In another specific embodiment, R^b and R^c form a six membered aromatic ring containing one or two nitrogen atoms according to formulas (IIb-d):



(IIb)



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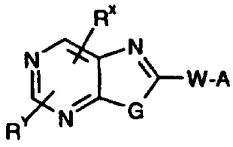
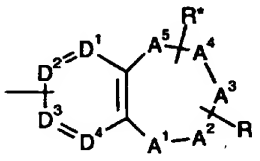


(IId)

wherein G, R^x and R^y are as above for formula (IIa).

Specifically, the compounds of this invention are comprised of a nitrogen-containing optionally fused five-membered ring, a linking group W, and a fibrinogen receptor antagonist template A. In particular, the fibrinogen receptor antagonist template A is as defined in Bondinell, et al., WO 93/00095, published January 7, 1993, of the sub-formula (VI):



(VI)

A^1 to A^5 form an accessible substituted seven-membered ring, which may be saturated or unsaturated, optionally containing up to two heteroatoms chosen from the group of O, S and N wherein S and N may be optionally oxidized;

D^1 to D^4 form an accessible substituted six membered ring, optionally containing up to two nitrogen atoms;

R is at least one substituent chosen from the group of R^7, or Q-C_{1-4}alkyl, Q-C_{2-4}alkenyl, Q-C_{2-4}alkynyl, optionally substituted by one or more of =O, R^{11} or R^7;

R^* is H, Q-C_{1-6}alkyl, Q-C_{1-6}oxoalkyl, Q-C_{2-6}alkenyl, Q-C_{3-4}oxoalkenyl, Q-C_{3-4}oxoalkynyl, Q-C_{2-4}alkynyl, C_{3-6}cycloalkyl, Ar or Het, optionally substituted by one or more of R^{11};

Q is H, C_{3-6}cycloalkyl, Het or Ar;

R^7 is -COR^8, -$COCR'_2R^9$, -$C(S)R^8$, -$S(O)_mOR'$, -$S(O)_mNR'R''$, -$PO(OR')$, -$PO(OR')_2$, -$B(OR')_2$, -NO_2 and Tet;

R^8 is -OR', -NR'R", -$NR'SO_2R'$, -NR'OR', -$OCR'_2C(O)OR'$, -$OCR'_2OC(O)$-R', -$OCR'_2C(O)NR'_2$, CF_3 or AA^1;

R^9 is -OR', -CN, -$S(O)_rR'$, $S(O)_mNR'_2$, -C(O)R' C(O)NR'_2 or -CO_2R';

R^{11} is H, halo, -OR^{12}, -CN, -$NR'R^{12}$, -NO_2, -CF_3, $CF_3S(O)_r$, -CO_2R', -$CONR'_2$, Q-C_{0-6}alkyl-, Q-C_{1-6}oxoalkyl-, Q-C_{2-6}alkenyl-, Q-C_{2-6}alkynyl-, Q-C_{0-6}alkyloxy-, Q-C_{0-6}alkylamino- or Q-C_{0-6}alkyl-$S(O)_r$-;

R^{12} is R', -C(O)R', -$C(O)NR'_2$, -$C(O)OR^{15}$, -$S(O)_mR'$ or $S(O)_mNR'_2$;

R^{13} is R', -CF_3, -SR', or -OR';

R^{14} is R', C(O)R', CN, NO_2, SO_2R' or $C(O)OR^{15}$;

R^{15} is H, C_{1-6}alkyl or Ar-C_{0-4}alkyl;

R' is H, C_{1-6}alkyl, C_{3-7}cycloalkyl-C_{0-4}alkyl or Ar-C_{0-4}alkyl;

R" is R', -C(O)R' or -$C(O)OR^{15}$;

R"' is R" or AA2;

AA1 is an amino acid attached through its amino group and having its carboxyl group optionally protected, and AA2 is an amino acid attached through its carboxyl group, and having its amino group optionally protected;

m is 1 or 2;

n is 0 to 3;

p is 0 or 1; and

t is 0 to 2; or

pharmaceutically acceptable salts thereof.

With reference to formula (VI), suitably,

A^1 is $CR^1R^{1'}$, CR^1, NR^1, N, O or $S(O)_x$;

A^2 is $CR^2R^{2'}$, CR^2, NR^2;

A^3 is $CR^3R^{3'}$, CR^3, NR^3, N, O or $S(O)_x$;

A^4 is $CR^4R^{4'}$, CR^4, NR^4, or N;

A^5 is $CR^5R^{5'}$, CR^5, NR^5, N, O or $S(O)_x$;

D^1-D^4 are CR^{11}, CR^6 or N;

R^1 and $R^{1'}$ are R^* or R, or together are =O;

R^2 and $R^{2'}$ are R^*, R or =O;

R^3 and $R^{3'}$ are R^*, R or =O;

R^4 and $R^{4'}$ are R^*, R or =O;

R^5 and $R^{5'}$ are R^*, R or =O; and

x is 0 to 2.

More suitably, A^1 is $CR^1R^{1'}$, CR^1, NR^1, N, O or S; A^2 is $CR^2R^{2'}$, NR^2 or CR^2; A^3 is $CR^3R^{3'}$; A^4 is $CR^4R^{4'}$, CR^4, NR^4, or N; A^5 is $CR^5R^{5'}$, CR^5, NR^5, N, O; D^1 - D^4 are CH; R^2 or R^4 are R; R^3,$R^{3'}$ and R^5,$R^{5'}$ are =O or R^*,H.

Preferably, A^1 is CHR^1, CR^1, NR", N or S; A^2 is CR^2 or $CR^2R^{2'}$; A^3 is $CR^3R^{3'}$; A^4 is $CR^4R^{4'}$ or NR^4; A^5 is $CR^5R^{5'}$, and D^1 - D^4 are CH.

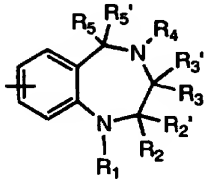
In one embodiment, A^1 is CR^1, A^2 is CR^2, A^3 is C=O, A^4 is NR^4 and A^5 are CHR^5.

In another embodiment, A^1 is NR^1, A^2 is $CHCR^2$, A^3 is $CR^3R^{3'}$, A^4 is NR^4, and A^5 are C=O.

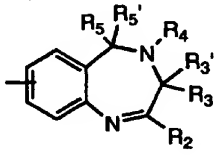
In yet another embodiment, A^1 and A^4 are C=O, A^2 is NR^2, A^3 is $CHR^{3'}$ and A^5 is NR^5.

In a preferred embodiment, A^1 is NR^1, A^2 is CHR^2, A^3 is C=O, A^4 is NR' and A^5 is CHR^5.

Representative sub-formulas of (VI) are given by each of formulas (VIa)-(VIi) below:



(VIa)



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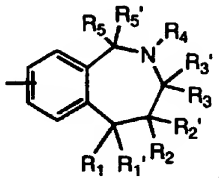

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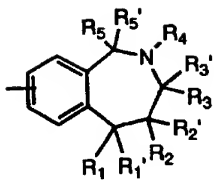

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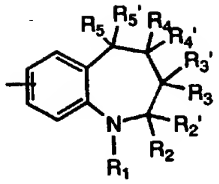
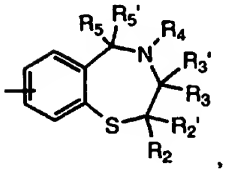
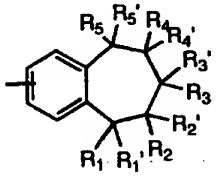


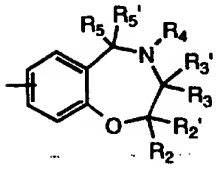
(VIe)



(VIf)

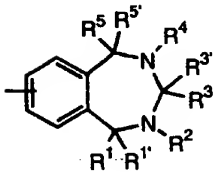


(VIg)



(VIh)

or



(VIi)

Specific embodiments of this invention wherein the fibrinogen receptor antagonist template A is of the sub-formula (VI) are named in the Examples.

Preferred compounds of this invention are:

5-[[[(Benzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-benzimidazole-2-aminoacetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]-methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[(5-trifluoromethylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(4,7-dimethoxybenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(4-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

S)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[N-(benzimidazol-2-yl)methyl-N-(2-cyanomethyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(4-phthalimidobutyl)-1H-1,4-benzodiazepine-2-acetic acid;

4-[[[3-(Benzimidazol-2-yl)propyl]amino]carbonyl]piperidine-1-acetic acid;

4-[[[3-(Benzimidazol-2-yl)propyl]amino]carbonyl]phenylacetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5,7-dimethylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]-carbonyl]-4-[2-(3,4-methylenedioxyphenyl)ethyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]-carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetamide;

(±)-2,3,4,5-Tetrahydro-7-[[[[1-[(benzimidazol-2-yl)methyl]benzimidazol-2-yl]methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[bis[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(4-azabenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[2-(benzimidazol-2-yl)acetyl]amino]-5-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(5,6-difluorobenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[bis[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-4-methyl-7-[[[(4-nitrobenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid;

(±)-4-[4-[[[(1H-Benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-phenylbutanoic acid;

(±)-3-[[[4-(4-Azabenzimidazol-2-yl)butanoyl]glycyl]amino]-4-pentynoic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[[1-(2-hydroxyethyl)benzimidazol-2-yl]methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(4-aminobenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

Ethyl (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate;

(S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid, [(2,2-dimethyl-2-methoxyacetyl)oxy]methyl ester;

2,3,4,5-Tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid;

(±)-N-[2-(Aminomethyl)-4-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]aspartic acid;

(±)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[(phenanthrimidazol-2-yl)methyl]amino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[3-(benzimidazol-2-yl)phenyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-4-[4-[[[(Benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-(dimethylaminocarbonyl)butanoic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-[2-(pyrid-3-yl)ethyl]-1H-1,4-benzodiazepine-2-acetate;

(S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-[[4-(2-carboxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-2-hydroxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;

Ethyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate;

2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-[[[(+)-biotinoyl]amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-(2RS)-acetic acid;

2,3,4,5-Tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(imidazo(1,2a)pyrid-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-5-[[2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepin-2-yl]methyl]tetrazole;

(S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[3-(benzimidazol-2-yl)propyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-(N-hydroxy)acetamide;

Ethyl (±)-3-[[[2-(Benzimidazol-2-yl)ethyl]amino]succinoyl]amino-4-pentynoate;

(±)-3-[[[2-(Benzimidazol-2-yl)ethyl]amino]succinoyl]amino-4-pentynoic acid;

(±)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-3-iodo-2-hydroxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;

2,3,4,5-Tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid;

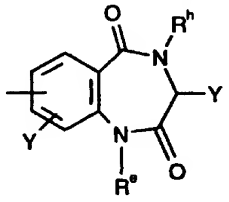
2,3,4,5-Tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid; and

(±)-7-[[[(4,5-Dimethyl-1H-imidazol-2-yl)methyl]methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
or pharmaceutically acceptable salts thereof.

The most preferred fibrinogen receptor antagonist template is of the sub-formula (VIa), wherein $CR^2R^{2'}$ is $CHCH_2CO_2H$, $CR^3R^{3'}$ is C=O, and $CR^5R^{5'}$ is CH_2. Vitronectin fibrinogen receptor antagonism is particularly pronounced when the A-W- substituent is attached to the 7-position of the 3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine ring system.

In the formula below the definitions for the substituents are as defined in formulas (I)-(V) and (XX)-(XXI), unless specified otherwise.

Another embodiment of a preferred fibrinogen receptor template A is represented by the 1,4-benzodiazepine 2,5-dione of sub-formula (VII);



(VII)

wherein:

Y is H, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, F, Cl, Br, I, CF_3, OR^f, $S(O)_kR^f$, COR^f, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, methylenedioxy, CN, CO_2R^f, $OC(O)R^f$, or $NHC(O)R^f$; and

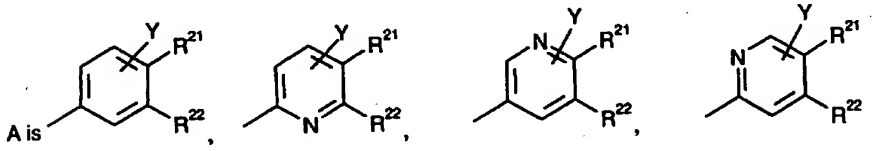
R^h is $(CH_2)_qCO_2R^f$.

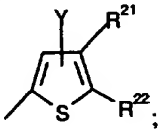
The preparation and the use of this sub-structure in preparing fibrinogen receptor antagonists of this sub-formula is detailed in Bondinell, et al., WO 93/00095 published January 7, 1993 and Blackburn, et al., WO 93/08174, published April 29, 1993.

Table I, below, summaries other preferred fibrinogen receptor templates that are included within the scope of the present invention. Such templates are:

Table I

(VIII)

A is 

or  ;

wherein:

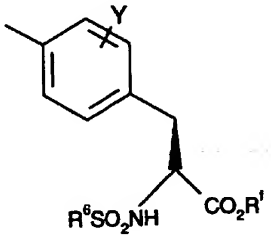
R^{21} and R^{22} independently are H or -Z-CO_2R^for Z-$CON(R^f)_2$ with the proviso that one of A^1 or A^2 is -Z-CO_2R^f or Z-$CON(R^f)_2$;

Z is -CH_2-, -$O(CH_2)_q$-, -$NR^f(CH_2)_q$-, -$S(CH_2)_q$, -CH_2CH_2-, -$CH(CH_3)CH_2$-, -$(CH_2)_3$-, -CH=CH-, -$C(CH_3)$=CH-, CH_2-CH=CH- or CH=$CHCH_2$; and

Y is H, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, F, Cl, Br, I, CF_3, OR^f, $S(O)_kR^f$, COR^f, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, methylenedioxy or Z-COR^f,

in Alig, et al., EP 0 381 033, published August 8, 1990.

(IX)



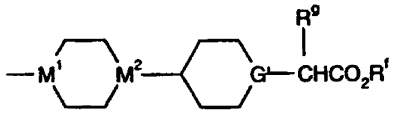
wherein:

R^6 is aryl, C_{1-10}alkyl, C_{3-6}cycloalkyl, C_{4-10}aralkyl, C_{1-10}alkoxyalkyl, C_{1-10}alkaryl, C_{1-10}alkylthioalkyl, C_{1-10}alkoxythioalkyl, C_{1-10}alkylamino, C_{4-10}aralkylamino, C_{1-10}alkanoylamino, C_{4-10}aralkanoylamino, C_{1-10}alkanoyl, C_{4-10}aralkanoyl, or C_{1-10}carboxyalkyl; and

Y is H, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, F, Cl, Br, I, CF_3, OR^f, $S(O)_kR^f$, COR^f, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, methylenedioxy, CN, CO_2R^f, $OC(O)R^f$, or $NHC(O)R^f$,

in Egbertson, et al., EP 0 478 328, published April 1, 1992.

(X)



wherein:

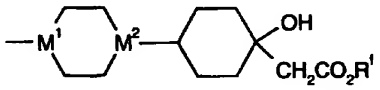
M^1 is CH or N;

M^2 is CH or N, with the proviso that when M^1 is CH, M^2 is N; and

G' is N or $N^{\oplus}R''$,

in Eldred, et al., EP 0542 363, published May 19, 1993.

(XI)



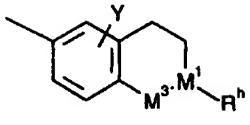
wherein:

M^1 is CH or N; and

M^2 is CH or N, with the proviso that when M^1 is CH, M^2 is N,

in Porter, et al., EP 0 537 980, published April 21, 1993.

(XII)



wherein:

M^1 is CH or N;

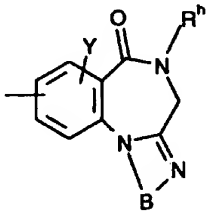
Y is H, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, F, Cl, Br, I, CF_3, OR^f, $S(O)_kR^f$, COR^f, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, methylenedioxy, CN, CO_2R^f, $OC(O)R^f$, or $NHC(O)R^f$;

D^3 is CH_2 or C=O; and

R^h is $(CH_2)_qCO_2R^f$,

in Klinnick, et al., EP 0 635,492, published January 25, 1995.

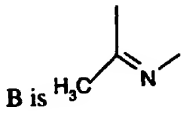
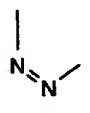
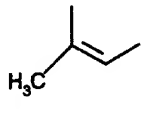
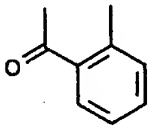
(XIII)



wherein:

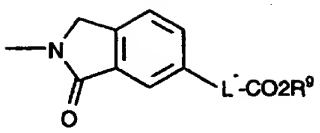
Y is H, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, F, Cl, Br, I, CF_3, OR^f, $S(O)_kR^f$, COR^f, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, methylenedioxy, CN, CO_2R^f, $OC(O)R^f$, or $NHC(O)R^f$;

R^h is $(CH_2)_nCO_2R^f$; and

B is  ,  ,  , or 

in Blackburn, et al., WO 95/04057, published February 9, 1995.

(XIV)

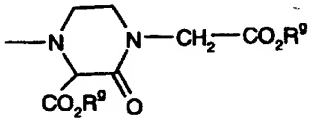


wherein:

L* is -C(O)NR^g-(CH_2)-, -C(O)-(CH_2)$_q$-, NR^g-(CH_2)$_q$-, -O-(CH_2)$_q$-, or S(O)$_k$-(CH_2)$_q$-,

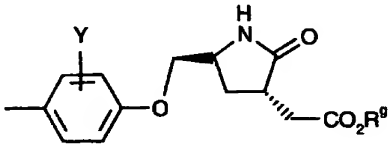
in Hartman, et al., EP 0 540 331, published May 5, 1993.

(XV)



in Sugihara, et al., EP 0 529,858, published March 3, 1993.

(XVI)

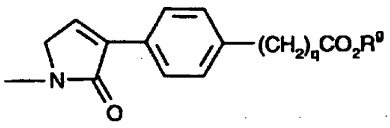


wherein:

Y is H, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, F, Cl, Br, I, CF_3, OR^f, S(O)$_k$R^f, COR^{f1}, NO_2, N(R^f)$_2$, CO(NR^f)$_2$, CH_2N(R^f)$_2$, methylenedioxy, CN, CO_2R^f, OC(O)R^f, or NHC(O)R^f,

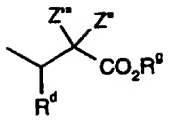
in Himmeisbach, et al., EP 0 483 667, published May 6, 1992.

(XVII)



in Linz, et al., EP 0 567 968, published November 3, 1993.

(XVIII)



wherein:

R^d is Het-C_{0-6}alkyl; and

Z", Z"' independently are hydrogen, C_{1-4}alkyl, halo, OR^f, CN, $S(O)_kR^f$, CO_2R^f, or OH,

in Bovy, et al., EP 0 539 343, published April 28, 1993.

Compounds of this invention comprising specific fibrinogen templates are named in the examples. These examples illustrate the invention, but do not limit the scope of the invention.

The above descriptions of fibrinogen receptor templates for use in the present invention were taken from pending published patent applications. Reference should be made to such patent applications for their full disclosures, including the methods of preparing said templates and specific compounds using said templates, the entire disclosure of such patent applications being incorporated herein by reference.

Table II, below, describes other fibrinogen receptor antagonists, whose core structures would be useful in carrying out the instant invention. Reference should be made to the patent applications and other publications for their full disclosures, including the methods of preparing said templates and specific compounds using said templates, the entire disclosure of the noted patent applications and other publications being incorporated herein by reference. Since it is contemplated that any fibrinogen receptor antagonist that is linked to an optionally fused nitrogen-containing five-membered ring will possess the novel utility described herein, the list below does not limit the scope of the present invention.

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In cases wherein the compounds of this invention may have one or more chiral centers, unless specified, this invention includes each unique nonracemic compound which may be synthesized and resolved by conventional techniques. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. The meaning of any substituent at any one occurrence is independent of its meaning, or any other substituent's meaning, at any other occurrence.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of this invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in *Eur. J. Biochem.*, 158, 9 (1984).

C_{1-4}alkyl as applied herein means an optionally substituted alkyl group of 1 to 4 carbon atoms, and includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl. C_{1-6}alkyl additionally includes pentyl, n-pentyl, isopentyl, neopentyl and hexyl and the simple aliphatic isomers thereof. C_{0-4}alkyl and C_{0-6}alkyl additionally indicates that no alkyl group need be present (*e.g.*, that a covalent bond is present).

Any C_{1-4}alkyl or C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or C_{1-6} oxoalkyl may be optionally substituted with the group R^x, which may be on any carbon atom that results in a stable structure and is available by conventional synthetic techniques. Suitable groups for R^x are C_{1-4}alkyl, OR', SR', C_{1-4}alkyl, C_{1-4}alkylsulfonyl,

C_{1-4}alkylsulfoxyl, -CN, $N(R')_2$, $CH_2N(R')_2$, $-NO_2$, $-CF_3$, $-CO_2R'$ $-CON(R')_2$, -COR', $-NR'C(O)R'$, OH, F, Cl, Br, I, N_3, or $CF_3S(O)_r$-,wherein r is 0 to 2.

Ar, or aryl, as applied herein, means phenyl or naphthyl, or phenyl or naphthyl substituted by one to three substituents, such as those defined above for alkyl, especially C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkthio, trifluoroalkyl, N_3, OH, CO_2H F, Cl, Br or I.

Het, or heterocycle, indicates an optionally substituted five or six membered monocyclic ring, or a nine or ten-membered bicyclic ring containing one to three heteroatoms chosen from the group of nitrogen, oxygen and sulfur, which are stable and available by conventional chemical synthesis. Illustrative heterocycles are benzofuran, benzimidazole, benzopyran, benzothiophene, biotin, furan, imidazole, indoline, morpholine, piperidine, piperazine, pyrrole, pyrrolidine, pyridine, tetrahydropyridine, pyridine, thiazole, thiophene, quinoline, isoquinoline, and tetra- and perhydro- quinoline and isoquinoline. Any accessible combination of up to three substituents on the Het ring, such as those defined above for alkyl that are available by chemical synthesis and are stable are within the scope of this invention.

C_{3-7}cycloalkyl refers to an optionally substituted carbocyclic system of three to seven carbon atoms, which may contain up to two unsaturated carbon-carbon bonds. Typical of C_{3-7}cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl and cycloheptyl. Any combination of up to three substituents, such as those defined above for alkyl, on the cycloalkyl ring that is available by conventional chemical synthesis and is stable, is within the scope of this invention.

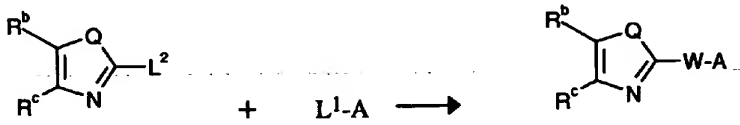
When R^b and R^c are joined together to form a five- or six-membered aromatic or non-aromatic carbocyclic or heterocyclic ring fused to the ring to which R^b and R^c are attached, the ring formed will generally be a five- or six-membered heterocycle selected from those listed above for Het, or will be a phenyl, cyclohexyl or cyclopentyl ring. Preferably R_b and R_c will be -D1=D2-D3=D4 wherein D1 - D4 are independently CH, N or C-R_x with the proviso that no more than two of D1 - D4

are N. Most preferably, when R^b and R^c are joined together they form the group -CH=CH-CH=CH-.

Certain radical groups are abbreviated herein. t-Bu refers to the tertiary butyl radical, Boc refers to the t-butyloxycarbonyl radical, Fmoc refers to the fluorenylmethoxycarbonyl radical, Ph refers to the phenyl radical, Cbz refers to the benzyloxycarbonyl radical, BrZ refers to the o-bromobenzyloxycarbonyl radical, ClZ refers to the o-chlorobenzyloxycarbonyl radical, Bzl refers to the benzyl radical, 4-MBzl refers to the 4-methyl benzyl radical, Me refers to methyl, Et refers to ethyl, Ac refers to acetyl, Alk refers to C_{1-4}alkyl, Nph refers to 1- or 2-naphthyl and cHex refers to cyclohexyl. Tet refers to 5-tetrazolyl.

Certain reagents are abbreviated herein. DCC refers to dicyclohexylcarbodiimide, DMAP refers to dimethylaminopyridine, DIEA refers to diisopropylethyl amine, EDC refers to 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride. HOBt refers to 1-hydroxybenzotriazole, THF refers to tetrahydrofuran, DIEA refers to diisopropylethylamine, DME refers to dimethoxyethane, DMF refers to dimethylformamide, NBS refers to N-bromosuccinimide, Pd/C refers to a palladium on carbon catalyst, PPA refers to 1-propanephosphonic acid cyclic anhydride, DPPA refers to diphenylphosphoryl azide, BOP refers to benzotriazol-1-yloxy-tris(dimethyl-amino)phosphonium hexafluorophosphate, HF refers to hydrofluoric acid, TEA refers to triethylamine, TFA refers to trifluoroacetic acid, PCC refers to pyridinium chlorochromate.

Compounds of the formula (I)-(V) are prepared, for example, by reacting a compound of formula (XIX) with a compound of formula (XX), wherein L^1 and L^2 are groups which may react to form a covalent bond in the moiety W, by methods generally known in the art.



(XIX) (XX) (I)

Typical methods include coupling to form amide bonds, nucleophilic displacement reactions and palladium catalyzed couplings. For instance, when W

contains an ether or amine linkage, the bond may be formed by a displacement reaction, and one of L^1 and L^2 will contain an amino or hydroxy group and the other will contain a displaceable group, such as a chloro, bromo or iodo group. When W contains an amide bond, typically one of L^1 and L^2 will contain an amino group, and the other will contain a carboxylic acid group. In another approach, L^1 may be an aryl or heteroaryl bromide, iodide or trifluoromethylsulfonyloxy derivative and L^2 may contain an amino group and the amide linkage may be formed by palladium-catalyzed aminocarbonylation with carbon monoxide in a suitable solvent such as dimethylformamide or toluene.

It will be apparent that the precise identity of L^1 and L^2 will be dependent upon the site of the linkage being formed. General methods for preparing the linkage $-(CHR")_r-U-(CHR")_s-V-$ are described, for example, in EP-A 0 372 486 and EP-A 0 381 033 and EP-A 0 478 363, which are incorporated herein by reference.

For instance, if V is CONH, L^1 may be $-NH_2$, L^2 may be OH (as in an acid) or Cl (as in an acid chloride), and $R^{6"}$ may be $W-(CR'_2)_q-Z-(CR'R^{10})_r-U-(CR'_2)_s-C(O)$, with any functional groups optionally protected. For example, $R^{6"}$ may be (benzyloxycarbonyl-amidino)benzoyl- or (N^{α}-Boc,N^{guan}-Tos)arginyl-. When L^2 is OH, a coupling agent is used.

Similarly, if V is NHCO, L^1 may be $-CO_2H$ or CO-Cl, L^2 may be $-NH_2$, and $R^{6"}$ may be $W-(CR'_2)_q-Z-(CR'R^{10})_r-U-(CR'_2)_s-$. For example, $R^{6"}$ may be (benzyloxycarbonyl-amidino)phenyl, (benzyloxycarbonylamino)methylbenzyl- or 6-(benzyloxycarbonylamino)hexyl-.

Where V is $NHSO_2$, L^1 may be SO_2Cl, L^2 may be $-NH_2$ and $R^{6"}$ may be as above. Where V is SO_2NH, L^1 may be $-NH_2$ and L^2 may be SO_2Cl. Methods to prepare such sulfonyl chlorides are disclosed, for instance, in *J. Org. Chem.*, 23, 1257 (1958).

If V is CH=CH, L^1 may be -CHO, L^2 may be $CH=P-Ph_3$ and $R^{6"}$ may be $W-(CR'_2)_q-Z-(CR'R^{10})_r-U-(CR'_2)_s-$. Alternately, L^1 may be $CH=P-Ph_3$, L^2 may be CHO, *e.g.*, $R^{6"}$ may be $W-(CR'_2)_q-Z-(CR'R^{10})_r-U-(CR'_2)_{s-1}-CHO$.

Where V is CH_2CH_2 may be obtained by reduction of a suitably protected compound wherein V is CH=CH.

Where V is CH_2O, CH_2N or $C\equiv C$, L^1 may be -OH, -NH or $-C\equiv CH$,respectively; L^2 may be -Br; and $R^{6''}$ may be $W\text{-}(CR'_2)_q\text{-}Z\text{-}(CR'R^{10})_r\text{-}U\text{-}(CR'_2)_s\text{-}$. For example, $R^{6''}$ may be (benzyloxycarbonylamino)-methylbenzyl- or 2-(N-benzyl-4-piperidinyl)-ethyl. Similarly where U or V is OCH_2, $NR'CH_2$ or $C\equiv C$, L^1 may be $-CH_2Br$ and L^2 may be -OH, -NH or $-C\equiv CH$, respectively. Alternately, when U or V is $C\equiv C$, L^1 may be Br, I or CF_3SO_3, L^2 may be $C\equiv CH$ and the coupling may be catalyzed by palladium and a base.

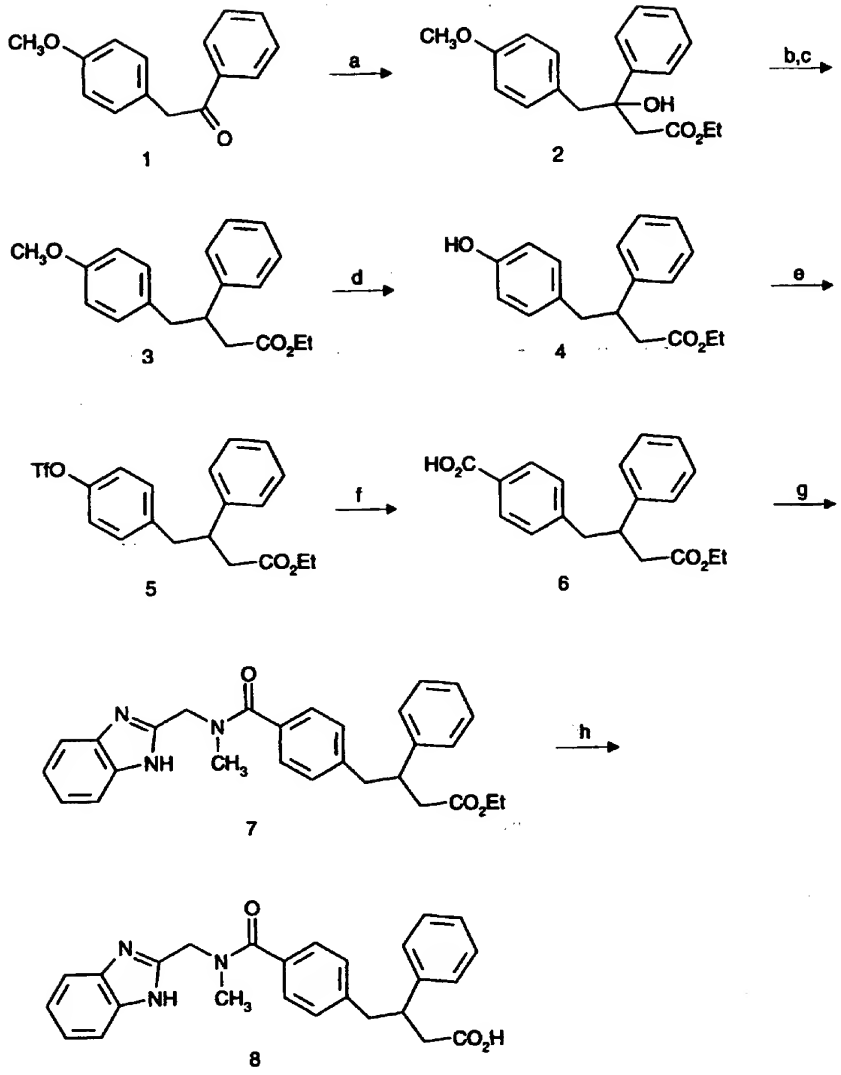
Compounds wherein V is $CHOHCH_2$ may be prepared from a suitably protected compound where V is CH=CH by the procedure disclosed in *J. Org. Chem.*, 54, 1354 (1989).

Compounds wherein V is CH_2CHOH may be obtained from a suitably protected compound where V is CH=CH by hydroboration and basic oxidation as disclosed in *Tet. Lett.*, 31, 231 (1990).

The core 6-7 fused ring system is prepared of formula (VI) by methods well known in the art, *e.g.*, Hynes, *et al.*, *J. Het. Chem.*, 1988, 25, 1173; Muller, *et al.*, *Helv. Chim. Acta.*, 1982, 65, 2118; Mori, *et al.*, *Heterocycles*, 1981, 16, 1491. Similarly, methods for preparing benzazepines, 1,4-benzothiazepines, 1,4-benzoxazepines and 1,4-benzodiazepines are known and are disclosed, for instance, in Bondinell, *et al.*, International Patent Application WO 93/00095.

The schemes which follow detail the preparation of the compounds of the instant invention.

Scheme I

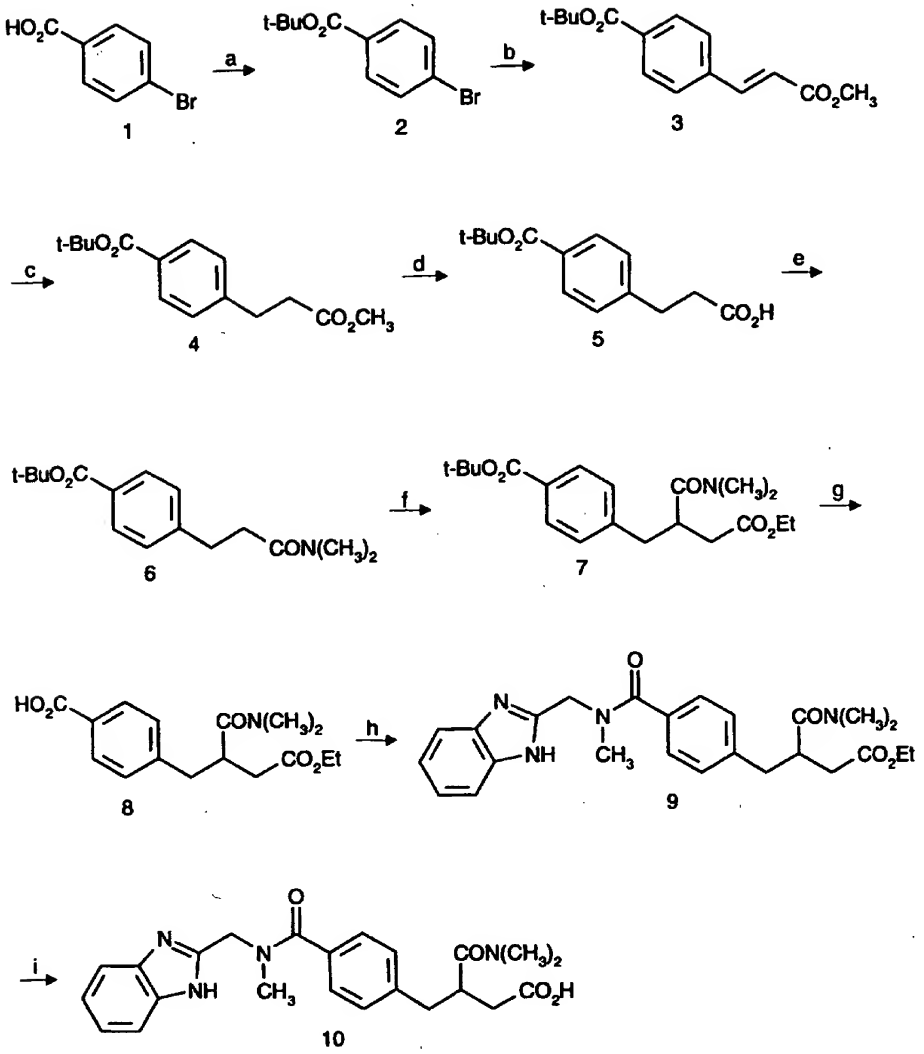


a) EtOAc/LiN(TMS)$_2$, THF; b) Et_3SiH, $BF_3 \cdot OEt_2$, CH_2Cl_2; c) H_2, 10% Pd/C, EtOH; d) EtSH, $AlCl_3$, CH_2Cl_2; e) Tf_2O, 2,6-lutidine, CH_2Cl_2; f) CO, KOAc, $Pd(OAc)_2$, dppf, DMSO; g) 2-(methylaminomethyl)benzimidazole dihydrochloride, EDC, $HOBt \cdot H_2O$, $(i\text{-}Pr)_2NEt$, CH_3CN; h) 1.0 N NaOH, EtOH.

An appropriately substituted deoxybenzoin, such as 2-(4-methoxyphenyl)-1-phenylethanone (*Chem. Ber.* **1958**, *91*, 755-759), is reacted in an aldol-type reaction with the enolate of ethyl acetate, which can be generated from ethyl acetate on exposure to an appropriate amide base, for instance lithium diisopropylamide (LDA) or lithium bis(trimethylsilyl)amide ($LiN(TMS)_2$), to afford **I-2**. Frequently, THF is the solvent of choice for an aldol reaction, although THF in the presence of various additives, for instance HMPA or TMEDA, is often used. Reaction of **I-2** with triethylsilane (Et_3SiH) in the presence of boron trifluoride etherate ($BF_3 \cdot OEt_2$) according to the general protocol of Orphanopoulos and Smonu (*Synth. Commun.* **1988**, 833) for the reduction of tertiary benzylic alcohols affords **I-3**, together with the olefinic product derived from β-elimination of the alcohol. The olefinic product can be conveniently converted to **I-3** by hydrogenation over a palladium catalyst, such as palladium metal on activated carbon (Pd/C), in an appropriate inert solvent, for instance methanol, ethanol, or ethyl acetate. Removal of the methyl ether of **I-3** to give **I-4** can be accomplished by reaction with ethanethiol (EtSH) in the presence of a Lewis acid catalyst, preferably anhydrous aluminum trichloride ($AlCl_3$), in an inert solvent, for instance CH_2Cl_2. Other useful methods for removal of a methyl ether are described in Greene, "Protective Groups in Organic Synthesis" (published by Wiley-Interscience). Alcohol **I-4** is converted to its trifluoromethanesulfonate ester **I-5** by reaction with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of a suitable non-nucleophilic amine base, such as 2,6-lutidine, in an inert solvent, generally CH_2Cl_2. **I-5** reacts with carbon monoxide (CO) in the presence of potassium acetate, 1,1'-bis(diphenylphosphino)ferrocene (dppf), and a palladium catalyst, for instance palladium acetate ($Pd(OAc)_2$), in a suitable solvent, preferably DMSO, according to the general method described by Cacchi and Lupi (*Tet. Lett.* **1992**, *33*, 3939) for the carboxylation of aryl trifluoromethanesulfonates. The resulting benzoic acid derivative **I-6** is converted to an activated form of the carboxylic acid using, for example, EDC and HOBt, or $SOCl_2$, and the activated form is subsequently reacted with an appropriate amine, for instance 2-(methylaminomethyl)methylbenzimidazole dihydrochloride, in a suitable solvent

such as DMF, CH_2Cl_2, or CH_3CN, to afford **I-7**. Depending on whether acid neutralization is required, an added base, such as diisopropylethylamine ($(i\text{-}Pr)_2NEt$) or pyridine, may be used. Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience), or Bodansky, "The Practice of Peptide Synthesis" (published by Springer-Verlag). The ethyl ester of **I-7** is hydrolyzed using aqueous base, for example, LiOH in aqueous THF or NaOH in aqueous methanol or ethanol, and the intermediate carboxylate salt is acidified with a suitable acid, for instance TFA or HCl, to afford the carboxylic acid **I-8**. Alternatively, the intermediate carboxylate salt can be isolated, if desired, or a carboxylate salt of the free carboxylic acid can be prepared by methods well-known to those of skill in the art.

Scheme II

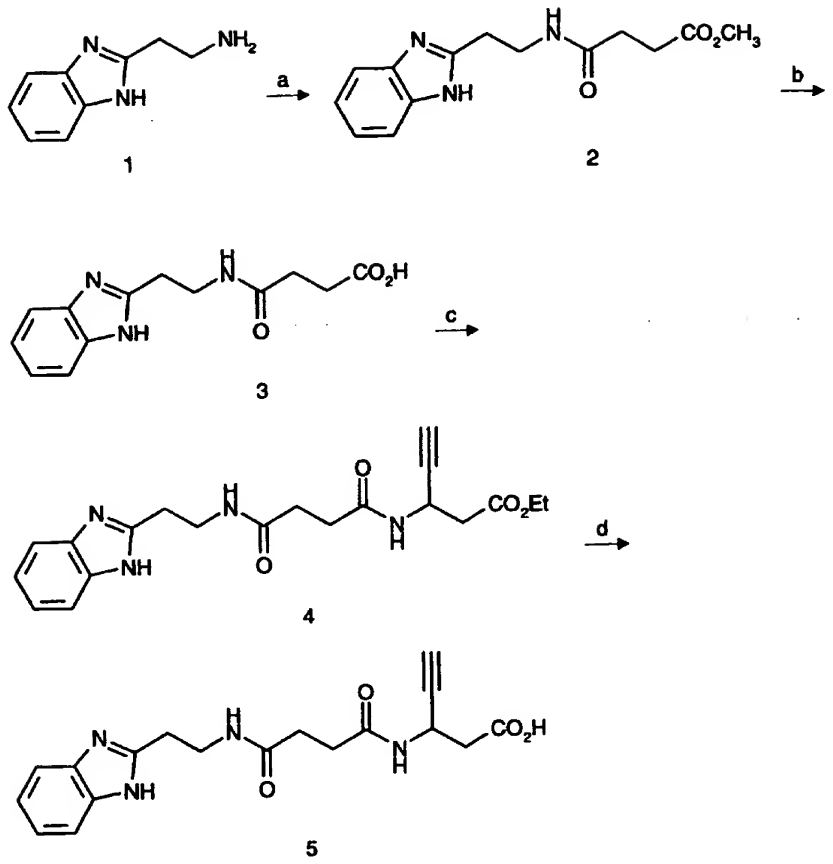


a) isobutylene, TfOH, CH_2Cl_2; b) methyl acrylate, $Pd(OAc)_2$, $P(tol)_3$, $(i\text{-}Pr)_2NEt$, propionitrile; c) H_2, 10% Pd/C, MeOH, EtOAc; d) 1.0 N LiOH, THF, H_2O; e) dimethylamine hydrochloride, EDC, HOBt · H_2O, $(i\text{-}Pr)_2NEt$, CH_3CN; f) $LiN(TMS)_2$, THF, then $BrCH_2CO_2Et$; g) TFA, CH_2Cl_2; h) 2-(methylaminomethyl)benzimidazole dihydrochloride, EDC, HOBt · H_2O, $(i\text{-}Pr)_2NEt$, CH_3CN; i) 1.0 N LiOH, THF, H_2O.

Commercially available 4-bromobenzoic acid (**II-1**) is converted to the tert-butyl ester **II-2** by reaction with isobutylene in the presence of a catalytic amount of an acid, such as trifluoromethanesulfonic acid (TfOH) or sulfuric acid, in an inert solvent, generally CH_2Cl_2 or diethyl ether. Alternative methods for the formation of tert-butyl esters are described in Greene, "Protective Groups in Organic Synthesis" (published by Wiley-Interscience). Other esters can be employed, as long as they are compatible with the subsequent chemistry and can be removed selectively when desired. A Heck-type reaction between **II-2** and methyl acrylate affords **II-3**. The general conditions for the Heck reaction have been reviewed by Heck (*Org. Reactions* **1982**, *27*, 345). For **II-2**, reaction with methyl acrylate in the presence of palladium (II) acetate ($Pd(OAc)_2$) and tri-ortho-tolylphosphine ($P(tol)_3$) in an inert solvent, such as CH_3CN, propionitrile, or toluene, in the presence of an appropriate acid scavenger, such as diisopropylethylamine ($(i\text{-}Pr)_2NEt$), affords **II-3**. Reduction of the α,β-unsaturated ester of **II-3** to afford the saturated compound **II-4** occurs under standard hydrogenation conditions, for instance reaction with hydrogen gas in the presence of a suitable catalyst, preferably palladium metal on activated carbon (Pd/C), in an inert solvent, generally methanol, ethanol, ethyl acetate, or mixtures thereof. The methyl ester of **II-4** is hydrolyzed using aqueous base, for example, LiOH in aqueous THF or NaOH in aqueous methanol or ethanol, and the intermediate carboxylate salt is acidified with a suitable acid, for instance TFA or HCl, to afford the carboxylic acid **II-5**. This is converted to an activated form of the carboxylic acid using, for example, EDC and HOBt, or $SOCl_2$, and the activated form is subsequently reacted with an appropriate amine, for instance dimethylamine hydrochloride, in a suitable solvent such as DMF, CH_2Cl_2, or CH_3CN, to afford **II-6**. Depending on whether acid neutralization is required, an added base, such as diisopropylethylamine ($(i\text{-}Pr)_2NEt$) or pyridine, may be used. Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience), or Bodansky, "The Practice of Peptide Synthesis" (published by Springer-Verlag). Reaction of **II-6** with an amide base, for

instance lithium bis(trimethylsilyl)amide ($LiN(TMS)_2$), sodium bis(trimethylsilyl)amide ($NaN(TMS)_2$), potassium bis(trimethylsilyl)amide ($KN(TMS)_2$), or lithium diisopropylamide (LDA), in an inert solvent, generally THF or ethylene glycol dimethyl ether (DME), affords an intermediate amide enolate. This is generally not isolated, but rather is reacted in situ with an electrophile, for example ethyl bromoacetate, to afford the alkylated product **II-7**. Various additives known to those of skill in the art, for instance HMPA, tetramethylethylenediamine (TMEDA), or 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), can be used to improve the efficiency of the alkylation reaction.). The tert-butyl ester group of **II-7** is removed under acidic conditions, generally with TFA or HCl, in an inert solvent, usually CH_2Cl_2, 1,4-dioxane, or mixtures thereof, to afford the acid **II-8**. Other useful methods for the removal of tert-butyl esters are described in Greene, "Protective Groups in Organic Synthesis" (published by Wiley-Interscience). **II-8** is converted to **II-9** under the general conditions described in Scheme I for the conversion of **I-6** to **I-7**, and **II-9** is converted to **II-10** by the general conditions described in Scheme I for the conversion of **I-7** to **I-8**.

Scheme III

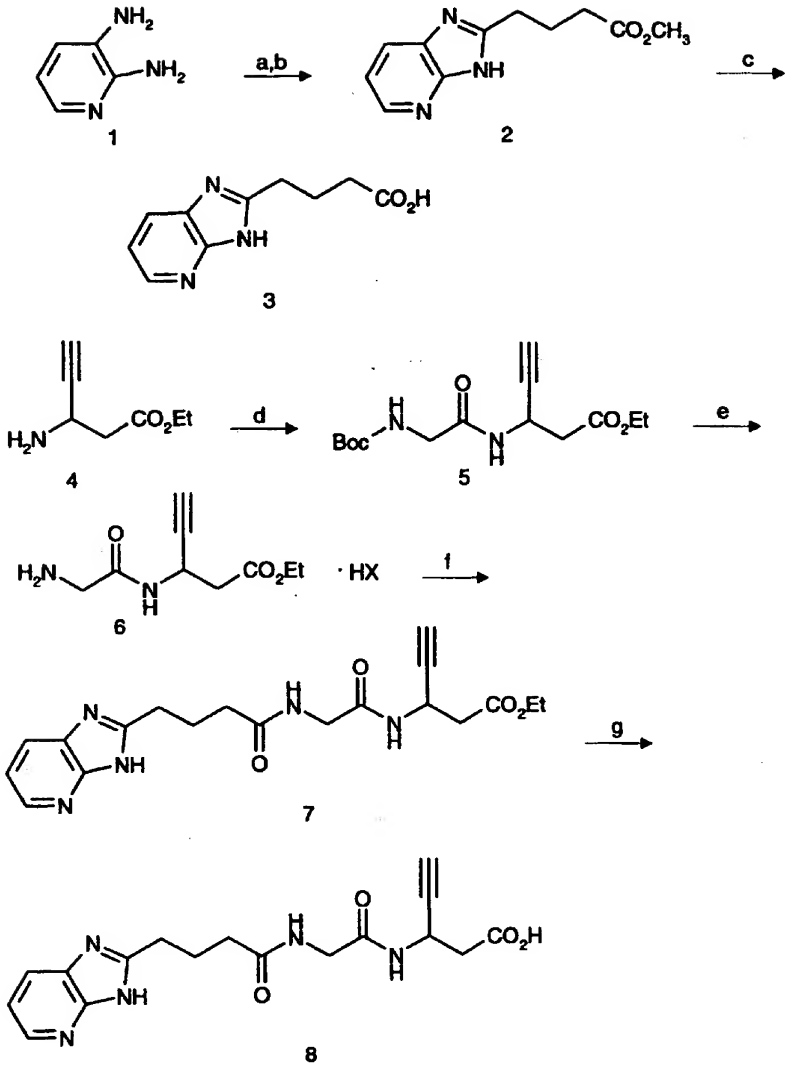


a) 3-carbomethoxypropionyl chloride, $(i\text{-}Pr)_2NEt$, CH_2Cl_2; b) 1.0 N NaOH, MeOH; c) ethyl 3-amino-4-pentynoate, EDC, HOBt · H_2O, $(i\text{-}Pr)_2NEt$, CH_3CN, DMF; d) 1.0 N LiOH, THF, H_2O, CH_3CN.

Readily available 2-(2-aminoethyl)benzimidazole is reacted with 3-carbomethoxypropionyl chloride in the presence of an appropriate acid scavenger, such as triethylamine, diisopropylethylamine, or pyridine, in a neutral solvent, generally CH_2Cl_2, to afford **III-2**. The methyl ester of **III-2** can be hydrolyzed to afford **III-3** under the general conditions described in Scheme 1 for the conversion

of **I-7** to **I-8**. Alternatively, **III-1** can be reacted with succinic anhydride in the presence of an appropriate base, such as triethylamine, diisopropylethylamine, or pyridine, in a neutral solvent, generally CH_2Cl_2, to afford **III-3** directly. **III-3** is converted to **III-4** by reaction with the known ethyl 3-amino-4-pentynoate (WO93/07867) under the general conditions described in Scheme I for the conversion of **I-6** to **I-7**. Hydrolysis of the ethyl ester of **III-4** to provide **III-5** is accomplished according to the general conditions conditions described in Scheme I for the conversion of **I-7** to **I-8**.

Scheme IV

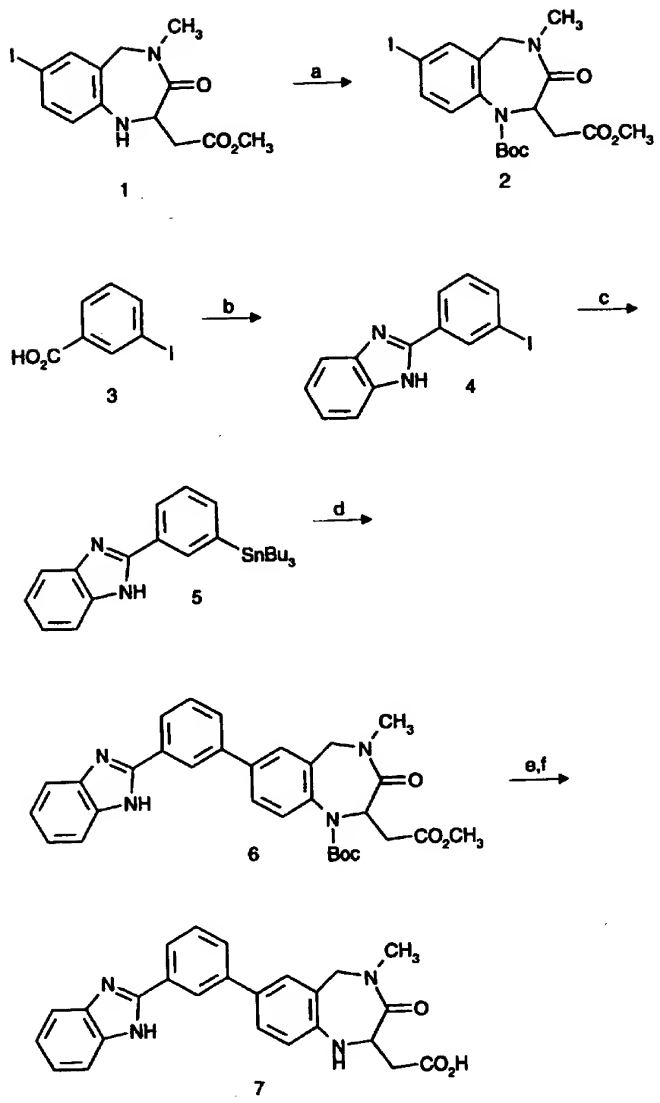


a) methyl 4-(chloroformyl)butyrate, Et_3N, THF; b) AcOH; c) 1.0 N NaOH, MeOH; d) Boc-Gly, EDC, HOBt · H_2O, $(i\text{-}Pr)_2NEt$, CH_3CN; e) TFA, CH_2Cl_2; f) **3**, EDC, HOBt · H_2O, $(i\text{-}Pr)_2NEt$, CH_3CN; g) 1.0 N LiOH, THF, H_2O.

The synthesis of **IV-8** is accomplished by the reaction of two separately prepared intermediates, **IV-3** and **IV-6**. The preparation of intermediate **IV-3** begins

with commercially available 2,3-diaminopyridine (**IV-1**). Accordinf to this scheme, **IV-1** is acylated with methyl 4-(choloroformyl)butyrate in the presence of a suitable acid scavenger, such as triethylamine, diisopropylethylamine, or pyridine, in a neutral solvent, generally CH_2Cl_2 or THF, to afford an intermediate monoacylated derivative. This derivative is then cyclized, for example using refluxing acetic acid, to afford **IV-2**. Hydrolysis of the methyl ester of **IV-2** under the general conditions described in Scheme 1 for the conversion of **I-7** to **I-8** affords **IV-3**. The preparation of the intermediate **IV-6** begins with the coupling of the known ethyl 3-amino-4-pentynoate (WO93/07867) with commercially available tert-butoxycarbonylglycine (Boc-Gly) under standard peptide bond forming conditions described in the previously referenced Bodansky publication, and in Scheme 1 for the conversion of **I-6** to **I-7**. The product of this reaction, **IV-5**, is deprotected to **IV-6** under acidic conditions which are known to effect removal of a Boc protecting group. Such conditions are described in the previously referenced Bodansky and Greene publications. The two intermediates **IV-3** and **IV-6** are coupled under standard peptide coupling conditions as previously described to afford **IV-7**, which is hydrolyzed to **IV-8** according to the general methods described in Scheme 1 for the conversion of **I-7** to **I-8**.

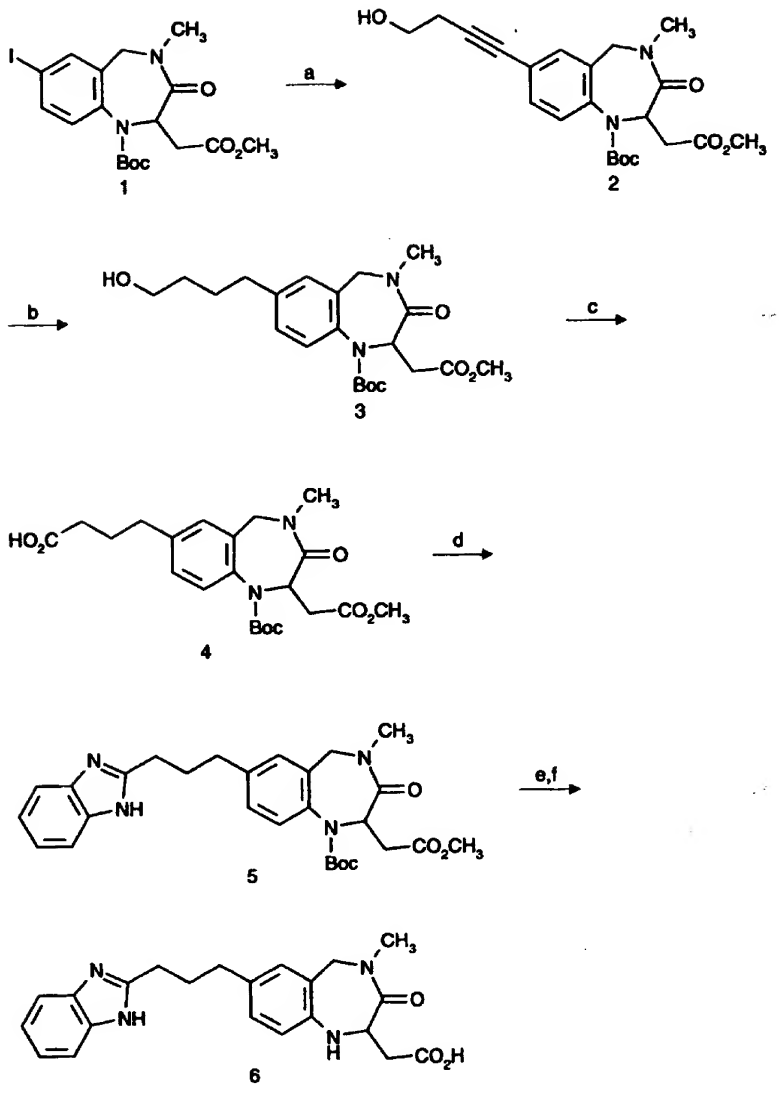
Scheme V



a) $(Boc)_2O$, DMAP, CH_3CN; b) isobutylchloroformate, Et_3N, THF, then 1,2-phenylenediamine, then AcOH; c) $(n\text{-}Bu_3Sn)_2$, $(PPh_3)_2PdCl_2$, DMF; d) CuI, $(PPh_3)_2PdCl_2$, DMF; e) 4 M HCl/dioxane; f) 1.0 N NaOH, MeOH.

The synthesis of **V-7** is accomplished by the reaction of two separately prepared intermediates, **V-2** and **V-5**. **V-2** is conveniently prepared by reaction of the readily available **V-1** with di-tert-butyl dicarbonate ($(Boc)_2O$) in the presence of an acylation catalyst, preferably 4-dimethylaminopyridine (DMAP) or 4-pyrrolidinopyridine, in a neutral solvent, for example CH_3CN, THF, or CH_2Cl_2. The preparation of intermediate **V-5** begins with commercially available 3-iodobenzoic acid (**V-3**), which is converted to the benzimidazole derivative **V-4**. According to this scheme, **V-3** is reacted with isobutyl chloroformate in the presence of a suitable amine base, such as triethylamine, diisopropylethylamine, or 4-methylmorpholine, in a neutral solvent, generally CH_2Cl_2 or THF, to afford an intermediate mixed anhydride derivative. Without isolation, this derivative is reacted with an appropriate phenylenediamine to produce a mono-N-acylated phenylenediamine intermediate. This intermediate is then cyclized to **V-4** using acetic acid. Reaction of **V-4** with bis(tributyltin) to produce **V-5** occurs under palladium catalysis using, for example bis(triphenylphosphine)palladium (II) chloride ($(PPh_3)_2PdCl_2$), in an inert solvent, usually DMF. Stille-type coupling of **V-2** with **V-5** to afford **V-6** is mediated by a palladium catalyst, for instance bis(triphenylphosphine)palladium (II) chloride ($(PPh_3)_2PdCl_2$), in the presence of copper (I) iodide (CuI), in a suitable neutral solvent, generally DMF. To obtain **V-7**, the protecting groups of **V-6** are removed by well-established methods known to those of skill in the art and described in the previously cited Greene publication. Thus, the Boc protecting group is removed under acidic conditions, such as 4 M HCl in dioxane or TFA in CH_2Cl_2, and the methyl ester is hydrolyzed as generally described in Scheme 1 for the conversion of **I-7** to **I-8**.

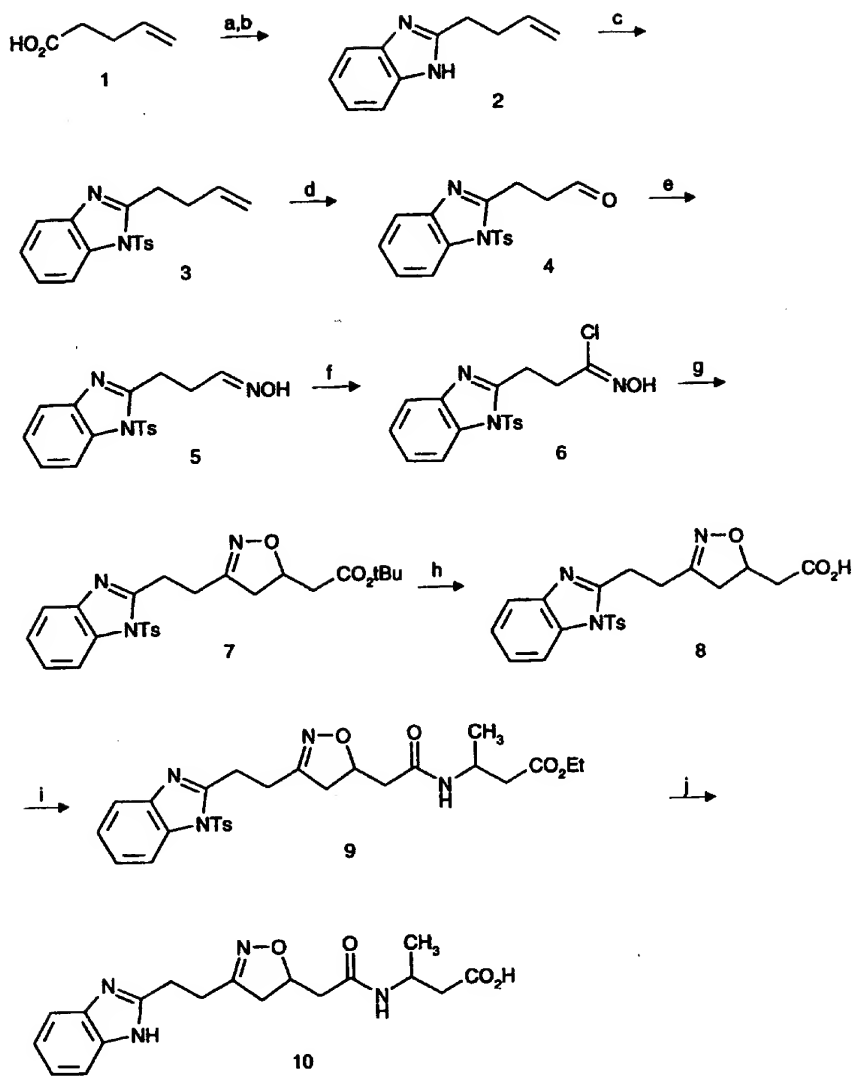
Scheme VI



a) 3-butyne-1-ol, $(PPh_3)_2PdCl_2$, PPh_3, CuI, Et_3N; b) H_2, 10% Pd/C, EtOH; c) 2,2,6,6-tetramethyl-oxopiperidinium chloride, CH_2Cl_2, then $NaClO_2$, Na_2HPO_3, 2-methyl-2-butene, H_2O; d) isobutyl chloroformate, Et_3N, then 1,2-phenylenediamine, then AcOH; e) 1.0 N LiOH, THF, H_2O; f) TFA, CH_2Cl_2.

Compound **VI-1**, the preparation of which is described in Scheme V, is reacted with 3-butyne-1-ol in the presence of a catalytic amount of a palladium salt, usually bis(triphenylphosphine)palladium (II) chloride ($(PPh_3)_2PdCl_2$), together with a catalytic amount of copper (I) iodide (CuI), in an amine solvent, such as triethylamine (Et_3N), to afford **VI-2**. A phosphine ligand, such as triphenylphosphine (PPh_3), can be added to improve the efficiency of the reaction. Reduction of the acetylenic unit of **VI-2** is accomplished under standard hydrogenation conditions which are well-known to those of skill in the art. The resulting compound, **VI-3**, is oxididized to the corresponding carboxylic acid **VI-4**, by the two-step method described by Wovkulich (*J. Org. Chem.* **1993**, *58*, 832-839). Many alternative methods for the oxidation of a primary alcohol to the corresponding carboxylic acid have been described, and can be found in such reference volumes as "Compendium of Organic Synthetic Methods" (published by Wiley-Interscience). Conversion of the carboxylic acid of **VI-4** to the benzimidazole derivative **VI-5** follows the procedures described in the above Schemes. The methyl ester of **VI-5** is removed as described in the above Schemes, and the Boc protecting group is removed under acidic conditions, such as 4 M HCl in dioxane or TFA in CH_2Cl_2, to afford **VI-6**.

Scheme VII

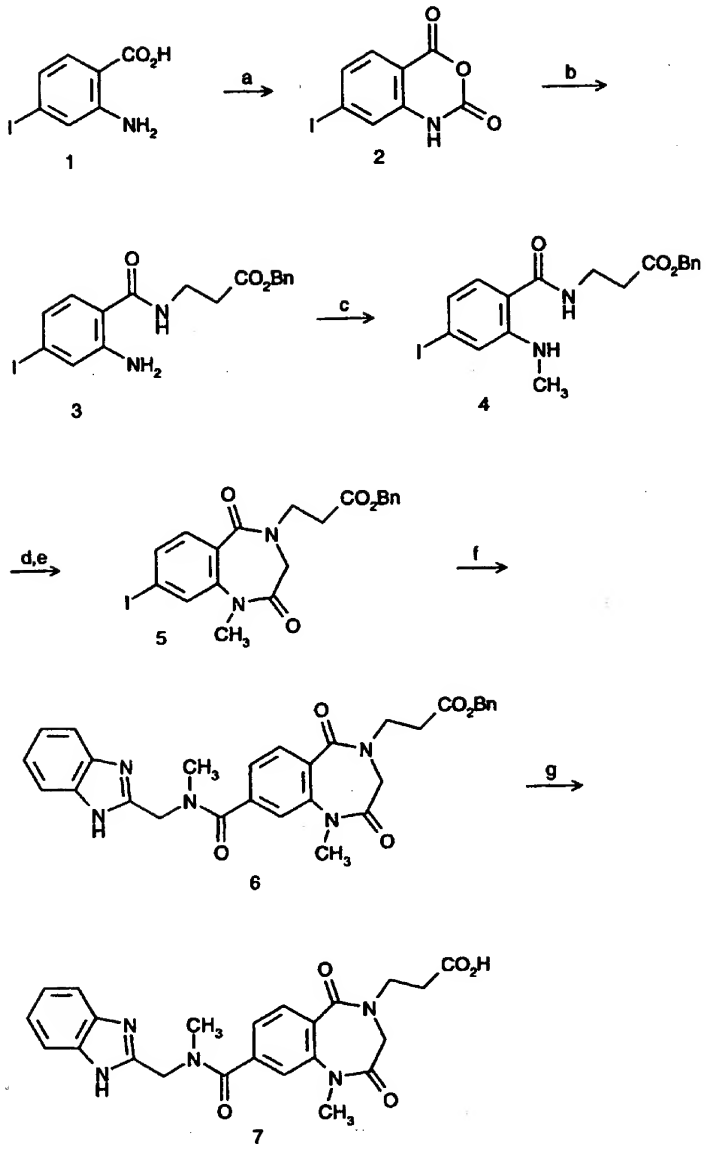


a) 1,2-phenylenediamine, DCC, DMF, CH_2Cl_2; b) AcOH, THF; c) TsCl, NaH, THF; d) O_3, CH_2Cl_2, MeOH, then DMS; e) $NH_2OH \cdot HCl$, NaOAc, MeOH; f) NCS, DMF; g) tert-butyl 3-butenoate, Et_3N; h) 4 M HCl/dioxane, CH_2Cl_2; i) ethyl 3-aminobutyrate, EDC, HOBt · H_2O, $(i\text{-}Pr)_2NEt$, CH_3CN; j) 1.0 N LiOH, THF, H_2O.

Commercially available 4-pentenoic acid (**VII-1**) is converted to the benzimidazole derivative **VII -2** using to the general procedures described previously. Protection of one of the nitrogen atoms of the benzimidazole moiety in **VII -2** can be accomplished by reaction with a sulfonyl chloride, for instance p-toluenesulfonyl chloride, in the presence of a suitable base, generally sodium hydride or an aqueous alkali metal hydroxide, in an inert solvent, preferably THF, to afford **VII -3**. Alternative protecting groups known to those of skill in the art may be used, as long as they are compatible with the subsequent chemistry and can be removed when desired. Such protecting groups are described in Greene, "Protective Groups in Organic Synthesis" (published by Wiley-Interscience). Oxidative cleavage of the olefin of **VII -3** to afford the aldehyde **VII -4** can be conveniently accomplished by ozonolysis in an inert solvent, usually CH_2Cl_2 or a mixture of CH_2Cl_2 and MeOH, followed by in-situ reduction of the ozonide with a suitable reducing agent, generally dimethylsulfide (DMS) or triphenylphosphine. Alternative methods for oxidative cleavage, such as the Lemieux-Johnson reaction (*J. Org. Chem.* **1956**, *21*, 478) can also be used. The aldehyde is converted to the aldoxime **VII -5** by standard procedures known to those of skill in the art, and this aldoxime is oxidized to the oximinoyl chloride derivative **VII -6** by the methods described in WO 95/14682 and WO 95/14683. Reaction of **VII -6** with an olefin, such as tert-butyl 3-butenoate (*Tet. Lett.* **1985**, *26*, 381-384), in the presence of a suitable base, for instance triethylamine or diisopropylethylamine, in an inert solvent such as benzene or toluene, according to the protocol described in WO 95/14682 and WO 95/14683, gives the cycloadduct **I-7**. The tert-butyl ester of **VII -7** is removed under standard acidic conditions, generally TFA in CH_2Cl_2 or HCl in dioxane, to give the carboxylic acid **VII -8**. The carboxylic acid is activated using, for example, EDC and HOBt, or $SOCl_2$, and the activated form is subsequently reacted with an appropriate amine, for instance a suitable derivative of β-alanine, in a neutral solvent, such as DMF, CH_2Cl_2, or CH_3CN, to afford **VII -9**. Depending on whether acid neutralization is required, an added base, such as diisopropylethylamine ($(i\text{-}Pr)_2NEt$) or pyridine, may be used. Many additional methods for converting a

carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience), or Bodansky, "The Practice of Peptide Synthesis" (published by Springer-Verlag). Derivatives of β–alanine are readily available in either racemic or optically pure form by a variety of methods known to those of skill in the art. A representative method is described in WO 93/07867. The ethyl ester and sulfonyl protecting groups of **VII -9** are removed using aqueous base, for example, LiOH in aqueous THF or NaOH in aqueous methanol or ethanol. The intermediate carboxylate salt is acidified with a suitable acid, for instance TFA or HCl, to afford the carboxylic acid **VII -10**. Alternatively, the intermediate carboxylate salt can be isolated, if desired, or a carboxylate salt of the free carboxylic acid can be prepared by methods well-known to those of skill in the art.

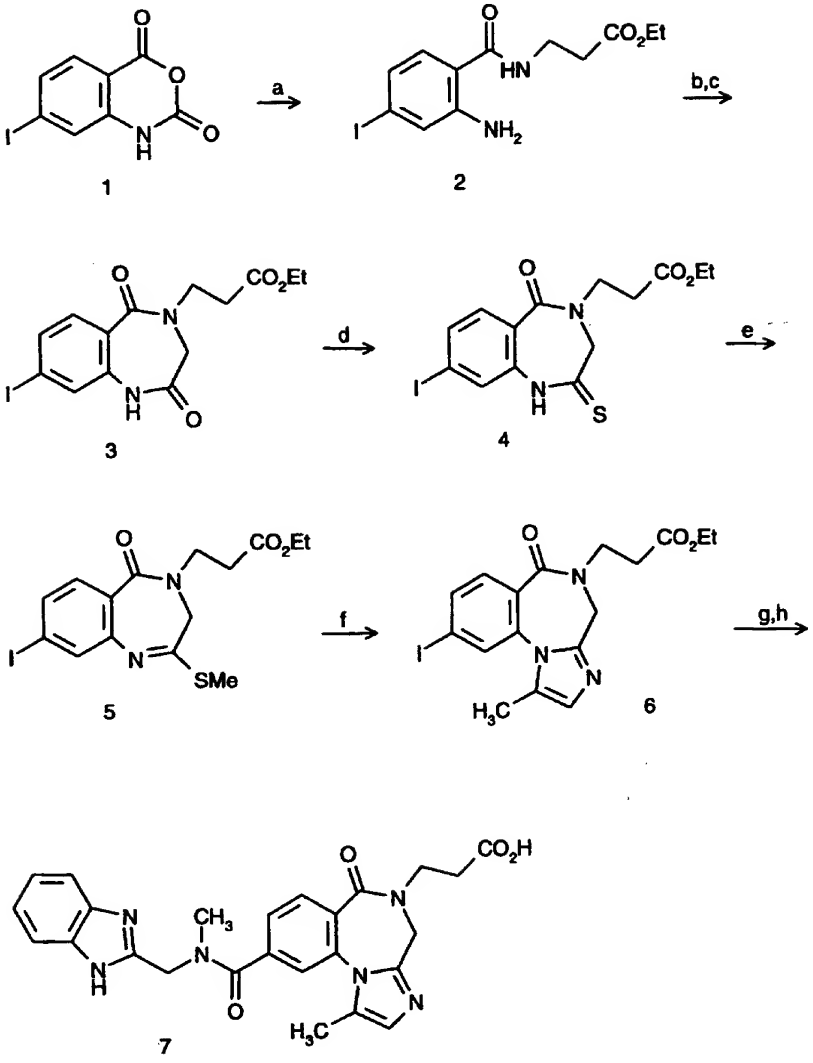
Scheme VIII



a) $COCl_2$ in toluene, Na_2CO_3, H_2O; b) β-alanine benzyl ester tosylate, DMAP, pyridine; c) CH_3I, 2,6-lutidine, DMF; d) $BrCH_2COBr$, Et_3N, CH_2Cl_2; e) NaH, DMF, f) CO, $(Ph_3P)_2PdCl_2$, DIEA, 2-(methylaminomethyl)benzimidazole dihydrochloride, NMP; g) H_2, Pd/C, EtOH.

Following the procedures of US 5403836 and WO 9504057, except starting from 2-amino-4-iodobenzoic acid (**VIII-1**) rather than 2-amino-5-iodobenzoic acid, compound **VIII -5** is prepared. Reaction of **VIII -5** with an appropriate amine, for instance 2-(methylaminomethyl)benzimidazole, in a carbon monoxide atmosphere, in the presence of a palladium catalyst, preferably $(Ph_3P)_2PdCl_2$, in an inert solvent, optimally 1-methyl-2-pyrrolidinone (NMP) gives the amide **VIII -6**. Depending on whether acid neutralization is required, an added base, such as diisopropylethylamine (DIEA) or pyridine, may be used. The benzyl ester of **VIII -6** is removed to afford **VIII -7** under standard hydrogenolysis conditions well-known to those of skill in the art. Alternatively, the benzyl ester can be saponified using aqueous base, for example, LiOH in aqueous THF, or NaOH in aqueous methanol or ethanol. The intermediate carboxylate salt is acidified with a suitable acid, for instance TFA or HCl, to afford the carboxylic acid. If desired, the intermediate carboxylate salt of **VIII -7** can be isolated, or a suitable salt of the carboxylic acid can be prepared by methods well-known to those of skill in the art.

Scheme IX

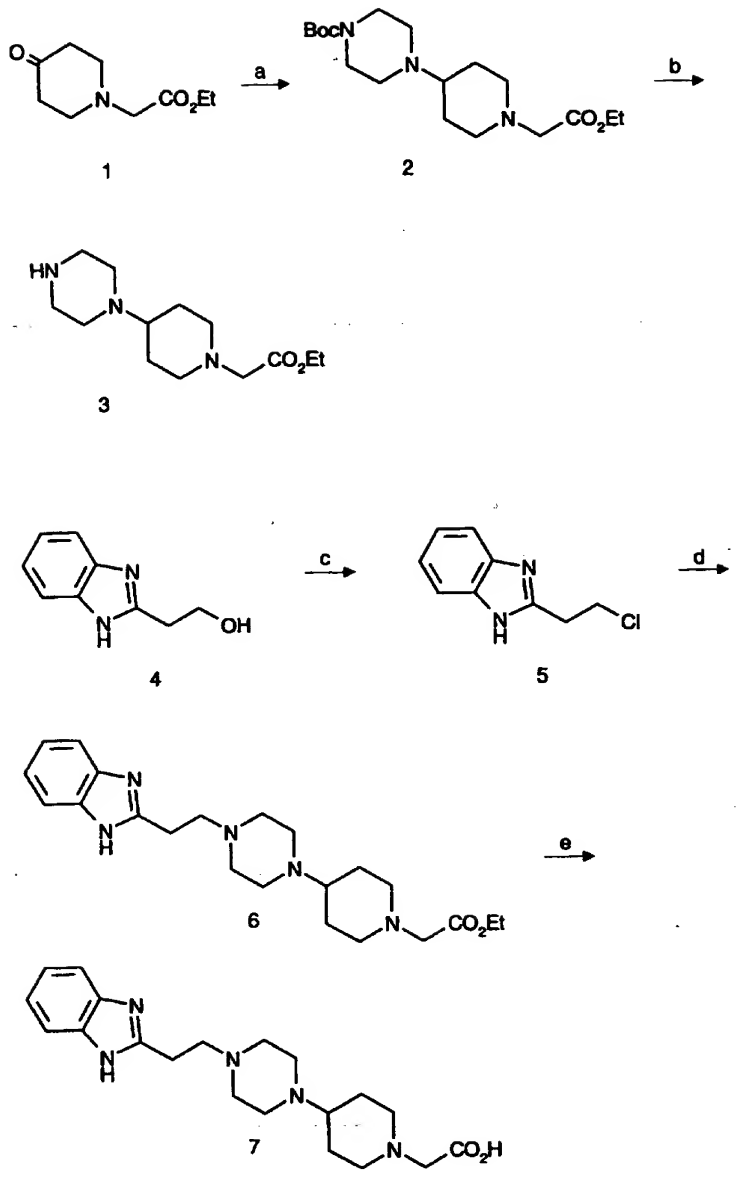


1 2 3 4 5 6 7

a) β-alanine ethyl ester hydrochloride, DMAP, pyridine; b) $BrCH_2COBr$, Et_3N, CH_2Cl_2; c) NaH, DMF; d) Lawesson's reagent, THF, 50° C; e) CH_3I, $(n\text{-}Bu)_4NHSO_4$, NaOH, CH_2Cl_2, H_2O; f) propargylamine, pyridine · HCl, toluene; g) CO, $(Ph_3P)_2PdCl_2$, DIEA, 2-(methylaminomethyl)benzimidazole dihydrochloride, NMP; h) LiOH, THF, H_2O.

Following the procedures of US 5403836 and WO 9504057, except starting from 4-iodoisatoic anhydride (**IX-1**, see Scheme I) rather than 5-iodoisatoic anhydride, compound **IX-6** is prepared. **IX-6** is converted to **IX-7** following the procedures described in Scheme XIII for the conversion of **XIII -5** to **XIII -7**.

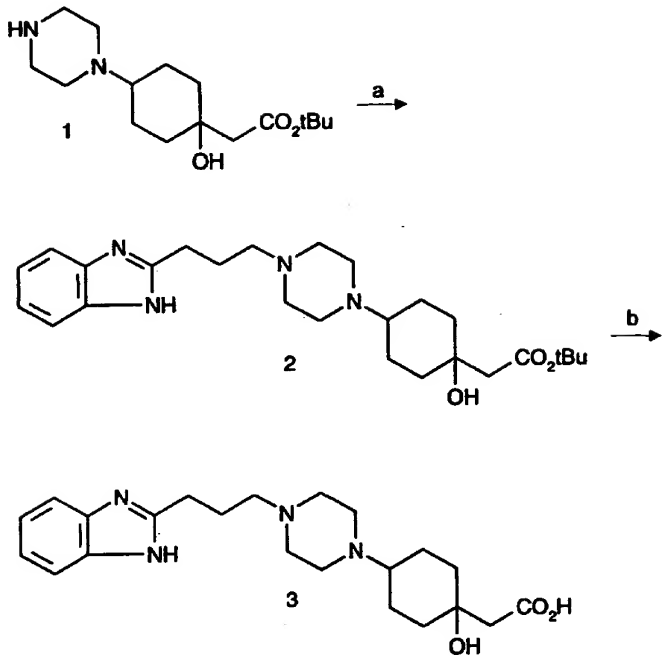
Scheme X



5 a) 1-Boc-piperazine, $NaBH_3CN$, HCl, MeOH; b) 4 M HCl/dioxane, CH_2Cl_2; c) $SOCl_2$, CH_2Cl_2; d) 3, DIEA, DMF; e) 1.0 N NaOH, MeOH.

Reductive amination of the readily available 1-(ethoxycarbonylmethyl)-4-piperidone (**X-1**, EPA 0 542 363 A2) with commercially available 1-Boc-piperazine and an appropriate reducing agent, preferably sodium cyanoborohydride, affords amine **X-2**. The reaction is generally conducted under acidic catalysis, usually with HCl, in a hydroxylic solvent, for instance methanol or ethanol. The Boc protecting group is removed under acidic conditions, preferably HCl/dioxane or TFA, in a suitable solvent, such as CH_2Cl_2, to the give amine **X-3**. This reacts with 2-(2-chloroethyl)benzimidazole (**X-5**) in the presence of an appropriate acid scavenger, for instance diisopropylethylamine (DIEA), in a polar solvent, preferably DMF, to give the coupled product **X-6**. 2-(2-Chloroethyl)benzimidazole can be prepared from 2-(2-hydroxyethyl)benzimidazole by reaction with a suitable halogenating reagent, such as thionyl chloride, or carbon tetrachloride in the presence of triphenylphosphine, in an inert solvent, for example CH_2Cl_2. The ethyl ester of **X-6** is removed using aqueous base, for example, LiOH in aqueous THF or NaOH in aqueous methanol or ethanol. The intermediate carboxylate salt is acidified with a suitable acid, for instance TFA or HCl, to afford the carboxylic acid **X-7**. Alternatively, the intermediate carboxylate salt can be isolated, if desired, or a carboxylate salt of the free carboxylic acid can be prepared by methods well-known to those of skill in the art.

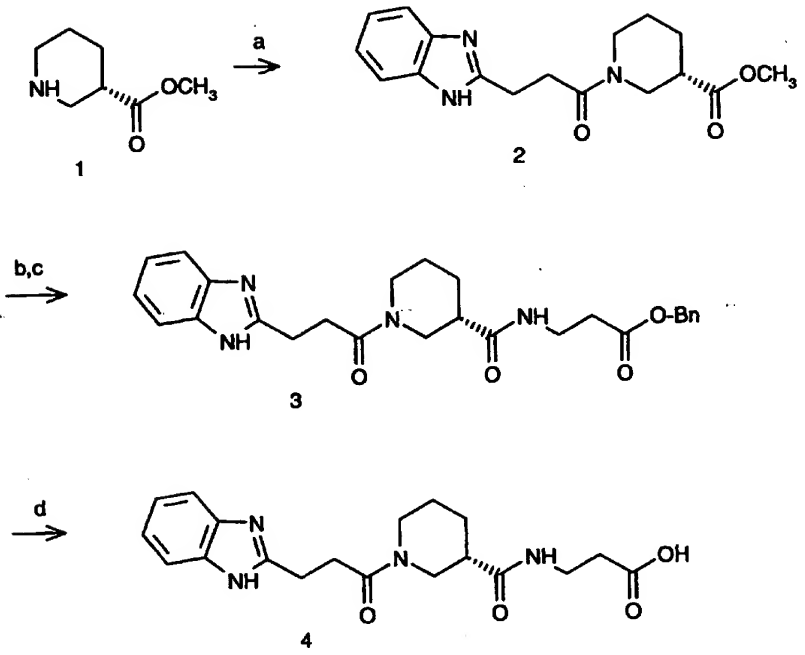
Scheme XI



a) 2-(3-bromopropyl)benzimidazole, DIEA, DMF; b) 4 M HCl/dioxane, CH_2Cl_2.

The readily available piperazine derivative **XI-1** (EPA 0 537 980 A1) is reacted with the readily available 2-(3-bromopropyl)benzimidazole (*J. Org. Chem.* **1962**, *27*, 2165) in the presence of an appropriate acid scavenger, for instance diisopropylethylamine (DIEA), in a polar solvent, preferably DMF, to give the coupled product **XI-2**. The tert-butyl ester protecting group is removed under standard acidic conditions, preferably HCl/dioxane or TFA, in a suitable solvent, such as CH_2Cl_2, to the carboxylic acid **XI-3**. If desired an appropriate salt of the carboxylic acid can be prepared by methods well-known to those of skill in the art.

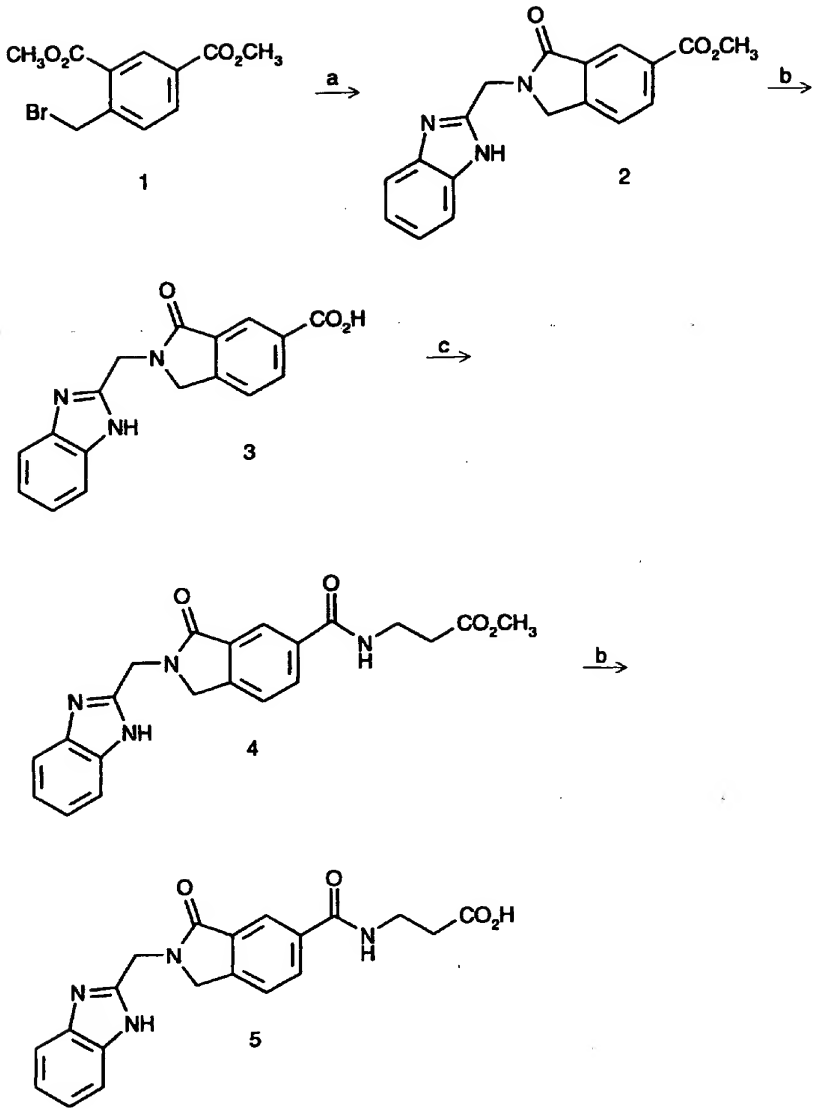
Scheme XII



a) 2-(benzimidazolyl)propionic acid, BOP-Cl, NMM, CH_2Cl_2; b) LiOH, THF, H_2O; c) benzyl β-alaninate, EDC, HOBt · H_2O, NMM, CH_2Cl_2; d) H_2, 10% Pd/C, AcOH, THF, H_2O.

The procedures of Beavers et. al., WO 95/25091, Example 1, were followed to give **XII-4**, except (2-benzimidazolyl)propionic acid was substituted for N^{α}-Boc-D-lys(Cbz)-OH.

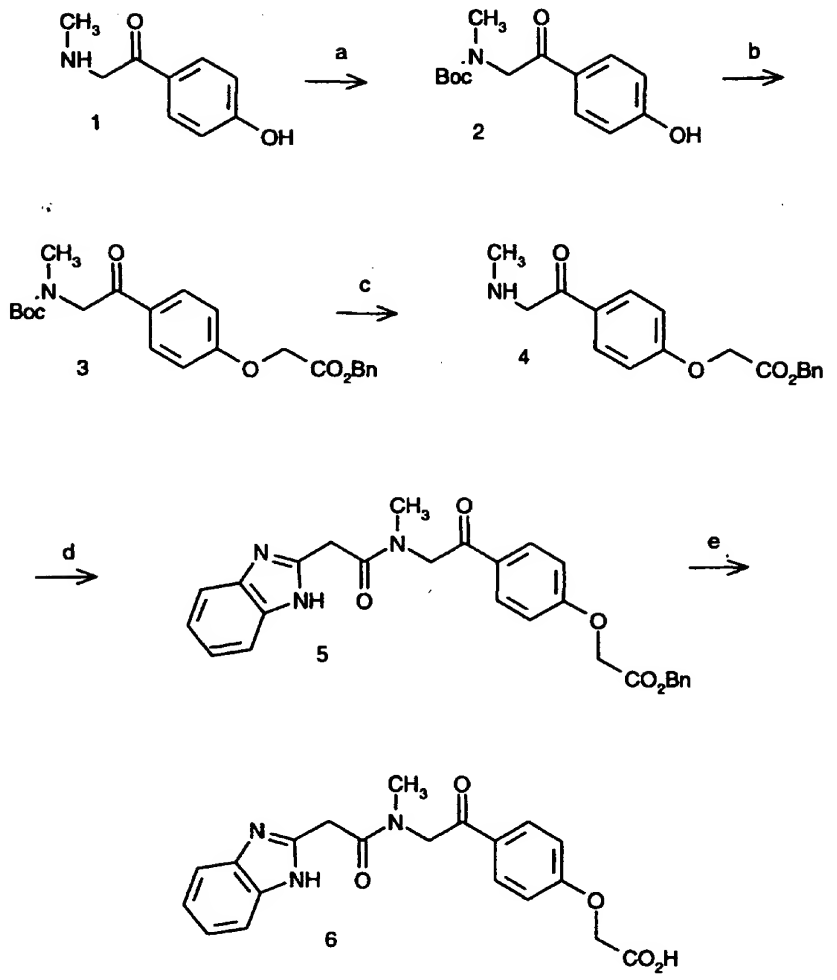
Scheme XIII



5 a) 2-(aminomethyl)benzimidazole, Et_3N, benzene; b) 1.0 N LiOH, MeOH, H_2O; c) β-alanine ethyl ester, BOP, Et_3N, CH_3CN.

A suitably functionalized amine, such as 2-(aminomethyl)benzimidazole, is reacted with dimethyl 4-bromomethylbenzene-1,3-dicarboxylate (**XIII-1**; synthesized as in EP 0540334A1) under the general conditions described for the preparation of 1-H-isoindole-5-carboxamide, 2,3-dihydro-N-(2-carboxy-ethyl)-2-[2-(piperidinyl)ethyl]-3-oxo (preparation 1-12, EPA 0 540 334 A1), to afford **XIII -2**. The methyl ester of **XIII -2** is hydrolyzed using aqueous base, for example, LiOH in aqueous THF or NaOH in aqueous methanol or ethanol, and the intermediate carboxylate salt is acidified with a suitable acid, for instance TFA or HCl, to afford the carboxylic acid **XIII -3**. The carboxylic acid of **XIII -3** is converted to an activated form of the carboxylic acid using, for example, EDC and HOBt, $SOCl_2$, or BOP reagent, and the activated form is subsequently reacted with an appropriate amine, for instance β-alanine ethyl ester, in a suitable solvent such as DMF, CH_2Cl_2, or CH_3CN, to afford **XIII -4**. Depending on whether acid neutralization is required, an added base, such as diisopropylethylamine ($(i\text{-}Pr)_2NEt$) or pyridine, may be used. Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience), or Bodansky, "The Practice of Peptide Synthesis" (published by Springer-Verlag). Ester hydrolysis as described above for the conversion of **XIII -2** to **XIII -3** then affords **XIII -5**. Alternatively, the intermediate carboxylate salt of **XIII -5** can be isolated, if desired, or a carboxylate salt of the free carboxylic acid can be prepared by methods well-known to those of skill in the art.

Scheme XIV

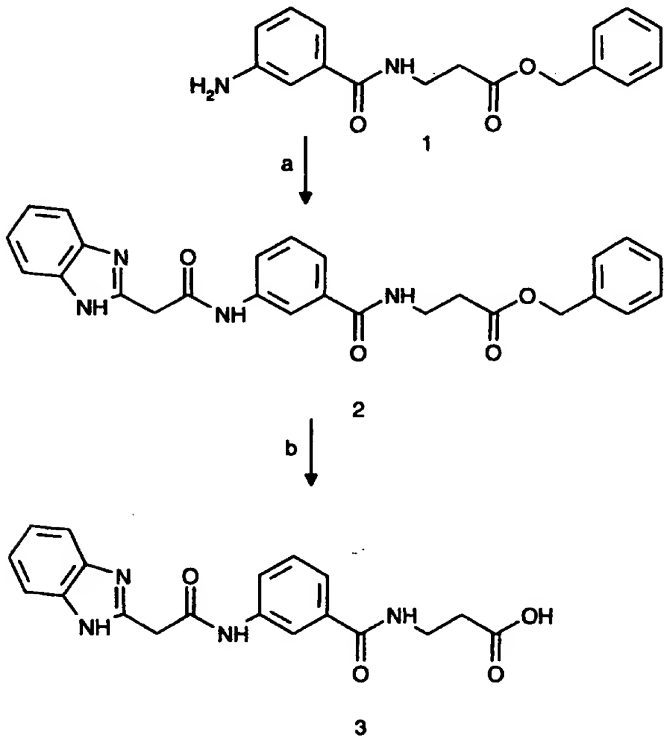


a) $(Boc)_2O$, NaOH, 1,4-dioxane, H_2O; b) $BrCH_2CO_2Bn$, K_2CO_3, acetone; c) 4 M HCl/dioxane; d) 2-(benzimidazolyl)acetic acid, EDC, DIEA, DMF; e) H_2, 5 % Pd/C, MeOH.

XIV-1 is treated with di-tert-butyl dicarbonate and sodium hydroxide in aqueous dioxane to afford **XIV -2**, which is alkylated on oxygen with benzyl bromoacetate and potassium carbonate in acetone to give **XIV -3**. The Boc group in

XIV -3 is removed with hydrogen chloride in dioxane, and the resulting **XIV -4** is acylated on nitrogen with 29benzimidazolyl)acetic acid, EDC and DIEA in DMF to give **XIV -5**. The benzyl ester in **XIV -5** is cleaved by treatment with hydrogen and palladium-on-carbon in methanol to give **XIV -6**.

Scheme XV

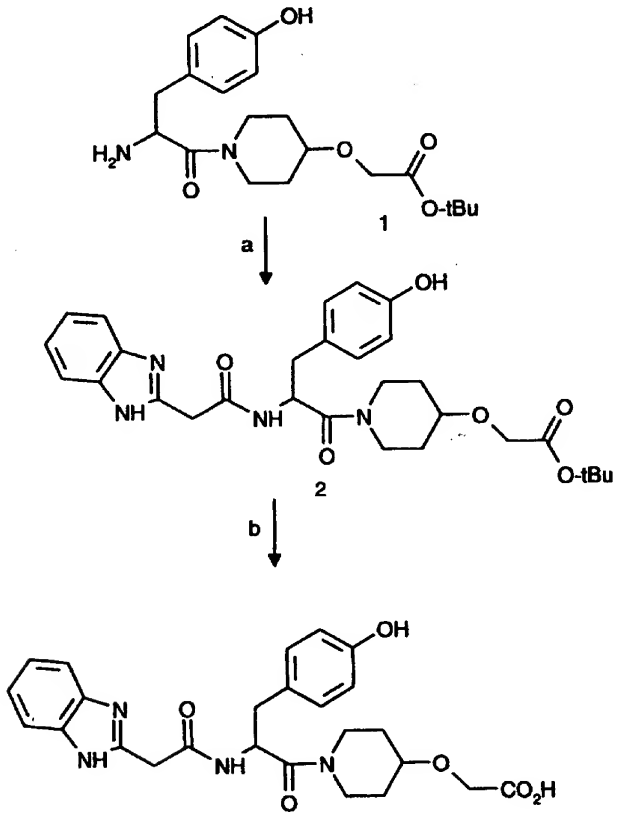


a) 2-(benzimidazolyl)acetic acid, EDC, DIEA, DMF; b) NaOH, H_2O, CH_3OH.

XI-1, prepared as described in Alig et. al., EPA 0372486, is condensed with a suitable substituted carboxylic acid, such (2-benzimidazolyl)acetic acid, in the presence of EDC and DIEA, and in a suitable solvent, e.g., DMF or acetonitrile.

Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthesis". Vol. I-VI (published by Springer-Verlag). Hydrolysis of the ester is accomplished by saponification with a suitable reagent, e.g., sodium hydroxide, in a suitable solvent, e.g., aqueous methanol. Alternatively, a benzyl ester may be converted to the acid by treatment with a suitable catalyst, e.g., Pd/C, and hydrogen in a suitable solvent, e.g., methanol, ethanol or acetic acid.

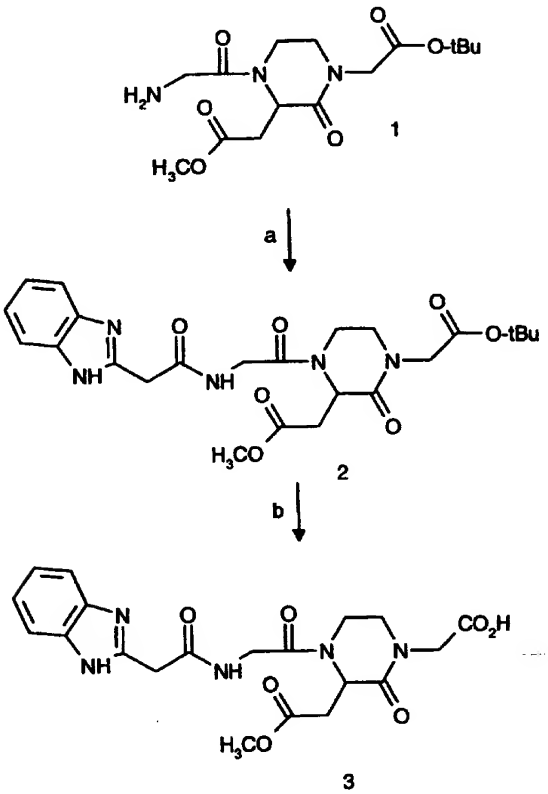
Scheme XVI



a) 2-(benzimidazolyl)acetic acid, EDC, DIEA, DMF; b) TFA

XVI-1, prepared as described in Alig et. al., EPA 0505868, is condensed with a suitable substituted carboxylic acid, such (2-benzimidazolyl)acetic acid, in the presence of EDC and DIEA, in a suitable solvent, e.g., DMF or acetonitrile, to give XVI -2. Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthesis". Vol. I-VI (published by Springer-Verlag). Hydrolysis of the ester in XVI -2 is accomplished with trifluoroacetic acid or hydrogen chloride to give XVI -3. Alternatively, the ester in XVI -2 may be saponified with a suitable reagent, e.g., 1N NaOH, in a suitable solvent, e.g., methanol.

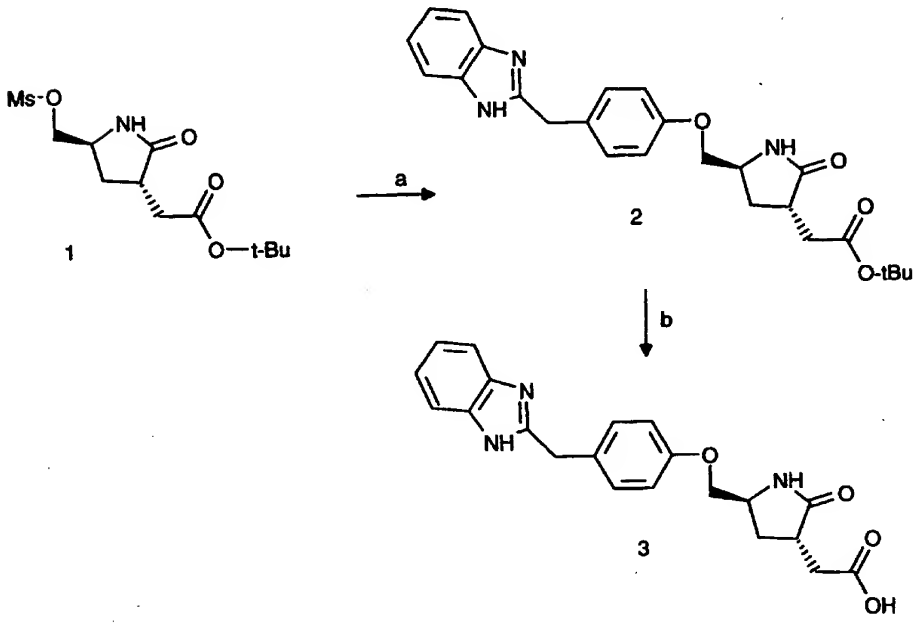
Scheme XVII



a) 2-(benzimidazolyl)acetic acid, EDC, DIEA, DMF; b) TFA, CH_2Cl_2.

XVII-1, prepared as described in Sugihara, et. al., EP 0529858, is condensed with a suitable substituted carboxylic acid, such as (2-benzimidazolyl)acetic acid, to give **XVII -2**, and the tert-butyl ester is cleaved with TFA, following the general procedure of Sugihara, et. al., Example 59, to give **XVII -3**. Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthesis", Vol. I-VI (published by Springer-Verlag).

Scheme XVIII

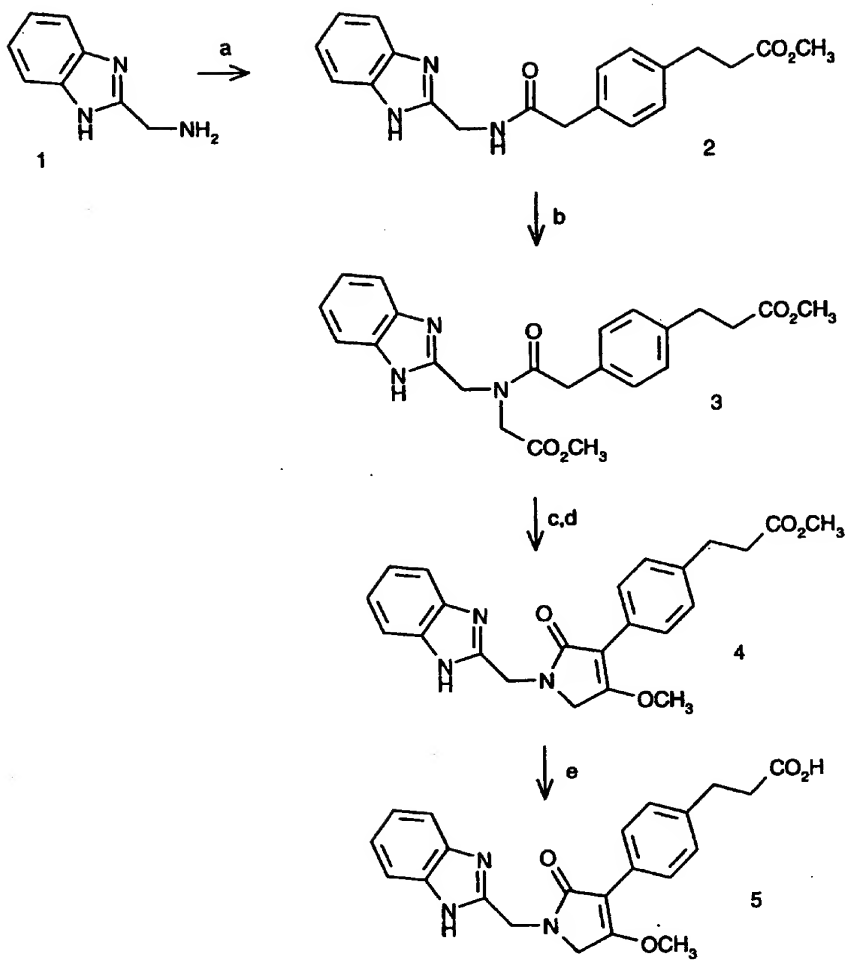


a) 4-[2-(benzimidazolyl)methyl]phenol, Cs_2CO_3, DMF; b) TFA

Compound **XVIII-1**, prepared as described in Himmelsbach, et. al., Australian Patent Application AU-A-86926/91, Example VI(28), is treated with a suitable substituted phenol, such as 4-[2-(benzimidazolyl)methyl]phenol, prepared

by the general procedure of Wahlgren and Addison, J. Heterocycl. Chem., **1989**, *26*, 541-3, following the general method of Himmelsbach, et. al., Example 3(51), to give **XVIII -2**. The tert-butyl ester in **XVIII -2** is hydrolyzed with 1N NaOH in CH_3OH following the general procedure of Himmelsbach, Example 7(3) to give **XVIII -3**. Alternatively, the tert-butyl ester may be cleaved with TFA or HCl.

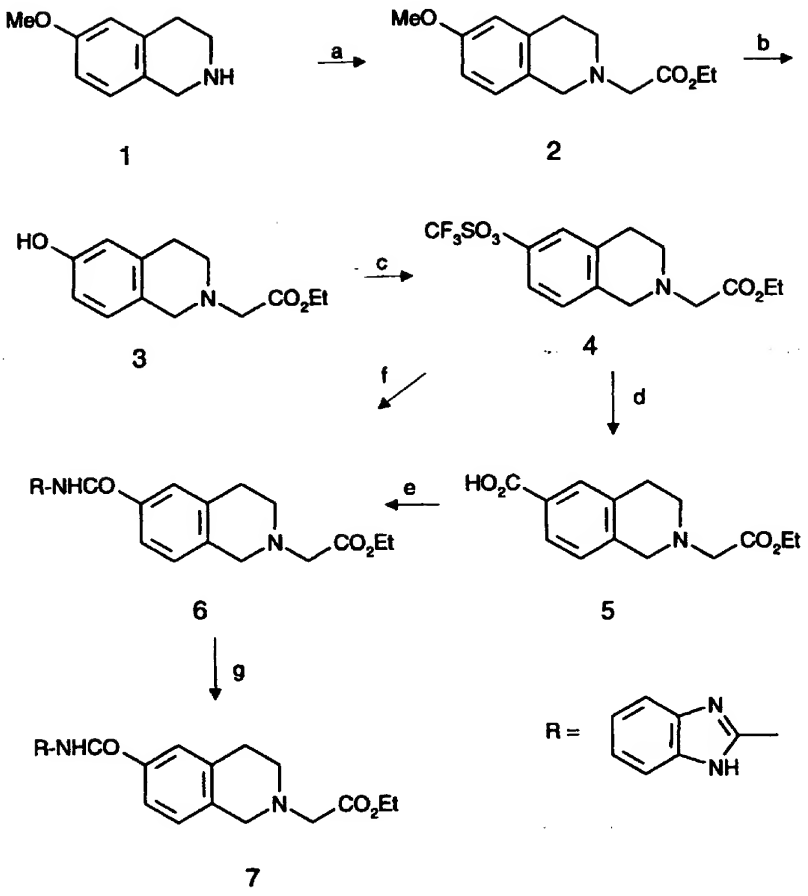
Scheme XIX



a) HO_2CCH_2Ph-4-$CH_2CH_2CO_2CH_3$, Ph_2POCl, Et_3N, DMAP, THF; b) NaH, DMF, $BrCH_2CO_2CH_3$; c) KOt-Bu, THF, DMF; d) KOt-Bu, CH_3I, DMF; e) LiOH, THF, H_2O.

The procedures of Linz, et. al., EP 0567968, are used to prepare XIX-5, except (2-benzimidazolyl)methanamine is substituted for 4-cyanoaniline.

Scheme XX

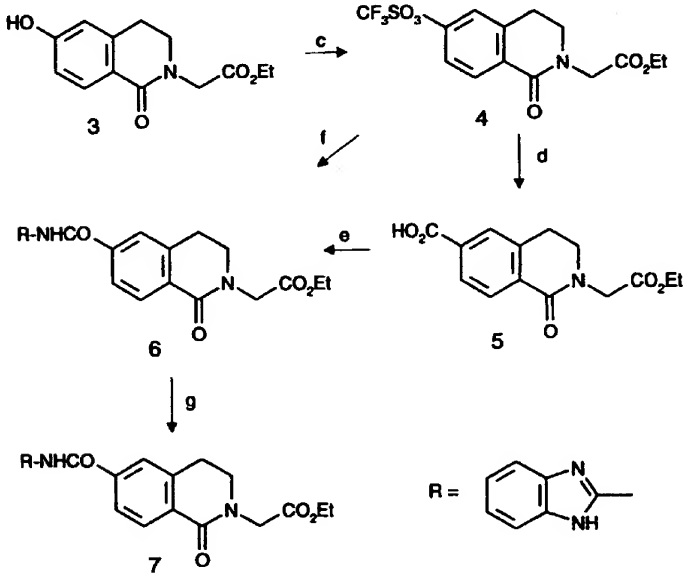


a) $ClCH_2CO_2Et$, Et_3N, DMF; b) BBr_3; c) $(CF_3SO)_2O$; d) CO, $Pd(OAc)_2$, PPh_3, DIEA, NMP, NH_4HCO_3, H_2O; e) H_2N-R, EDC / HOBt, DIEA, DMF; f) H_2N-R, CO, $Pd(OAc)_2$, PPh_3, DIEA, NMP, NH_4HCO_3, H_2O; g) 1N NaOH, HOEt

Scheme XX provides a method for the preparation of 1,2,3,4-tetrahydroisoquinoline compounds as exemplary fibrinogen receptor antagonists, as described in M. J. Fisher *et al.* (EP 0635492, Jan. 25, 1995). Accordingly, a 6-methoxy-3,4-dihydroisoquinoline, such as compound **XX-1** is prepared by the method described by D. J. Sall and G. L. Grunewald (J. Med. Chem. *1987*, 30,

2208-2216). The isoquinoline is treated with a haloacetic acid ester in the presence of a tertiary amine to afford the 2-acetic acid ester, as exemplified by compound **XX-2**. The 6-methoxy compound is converted into the corresponding 6-hydroxy compound by methods known in the art, for example with BBr_3, which is converted into the triflate with trifluorosulfonic acid anhydride. Palladium catalyzed carbonylation affords the 6-carboxy compound, such as compound **XX-5**, which is then condensed with an amine, as exemplified by (2-benzimidazolyl)acetic acid, employing a standard amide bond forming reagent to give the desired amide, such as compound **XX-6**. Saponification affords **XX-7**. Alternatively, the palladium catalyzed carbonylation reaction with the triflate, exemplified by compound **XX-4**, may be trapped with said aminomethyl compound to provide, after saponification, the corresponding 6-(2-benzimidazolyl)methylaminocarbonyl compound, **XX-7**.

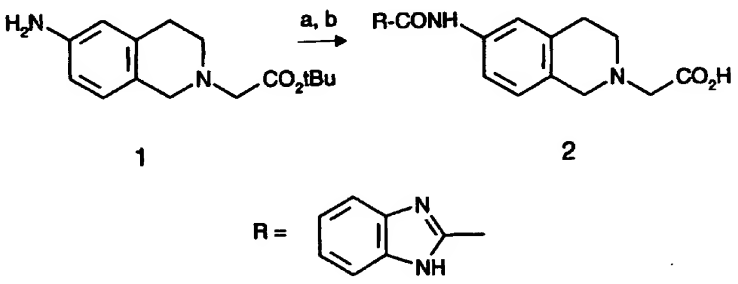
Scheme XXI



a) 1. $LiN(TMS)_2$, 2. $ClCH_2CO_2Et$, DMF; b) BBr_3; c) $(CF_3SO_2)_2O$; d) CO, $Pd(OAc)_2$, PPh_3, DIEA, NMP, NH_4HCO_3, H_2O; e) H_2N-R, EDC / HOBt, DIEA, DMF; f) H_2N-R CO, $Pd(OAc)_2$, PPh_2, DIEA, NMP, NH_4HCO_3, H_2O; g) 1N NaOH, HOEt

Scheme XXI provides a method for the preparation of 3,4-dihydroisoquinolin-1-one compounds as exemplary fibrinogen receptor antagonists, as described M. J. Fisher *et al.* (EP 0635492, Jan. 25, 1995). Accordingly, the 1-oxo compound **XXI-1**, prepared by the method described by D. J. Sall and G. L. Grunewald (J. Med. Chem. *1987*, 30, 2208-2216), is treated with a base, such as $LiN(TMS)_2$, and a haloacetic acid eser to give a 2-acetic acid ester, as exemplified by compound **XXI-2**. The 1-oxo compound is then employed in the analogous series of reactions deployed in Scheme XX, substituting the corresponding 1-oxo analog, as shown in Scheme XXI, to provide **XXI-7**. As in Scheme XX, alternatively, the palladium catalyzed carbonylation reaction with the triflate, exemplified by compound **XXI-4**, may be trapped with an amine to provide, after saponification, the amide, **XXI-7**.

Scheme XXII

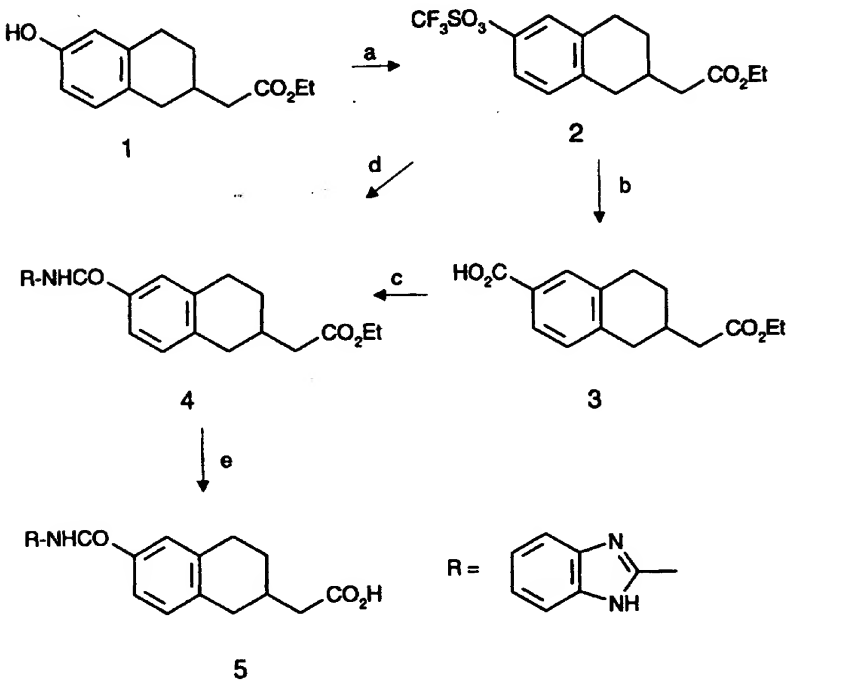


a) RCO-X; b) TFA / CH_2Cl_2

Scheme XXII provides a method for the preparation of 6-acylaminotetraline compounds as exemplary fibrinogen receptor antagonists, as described M. J. Fisher *et al.* (EP 0635492, Jan. 25, 1995). Accordingly, a 6-amino-2-tert-butyloxycarbonyl-tetral-1-one, exemplified by compound **XXII-1**, which is prepared according to the methods described in M. J. Fisher *et al.* (EP 0635492, Jan. 25, 1995), is condensed with an activated derivative of a carboxylic acid, such as the

activated derivative of (2-benzimidazolyl)acetic acid, to provide, after deesterification, the amide, **XXII-2.**

Scheme XXIII

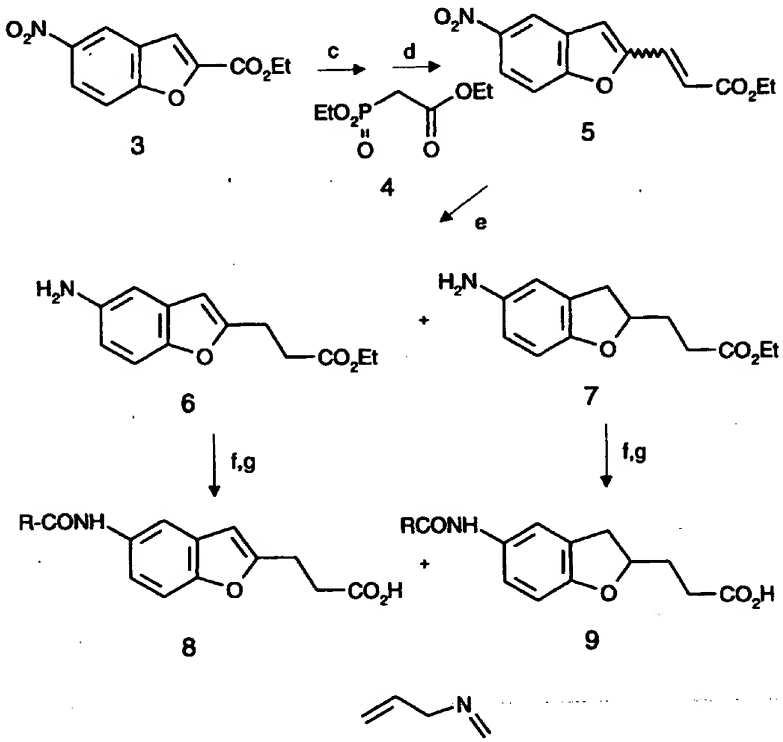


a) CF_3SO_2O; b) CO, $Pd(OAc)_2$, PPh3, DIEA, NMP, NH_4HCO_3, H_2O; c) H_2N-R, EDC / HOBt, DIEA, DMF; d) H_2N-R, CO, $Pd(OAc)_2$, PPh3, DIEA, NMP, NH_4HCO_3, H_2O; e) 1N NaOH, HOEt

Scheme XXIII provides a method for the preparation of 6-aminoacyltetraline compounds as exemplary fibrinogen receptor antagonists, as described M. J. Fisher *et al.* (EP 0635492, Jan. 25, 1995). Accordingly, an ethyloxycarbonylmethyl-6-hydroxy-tetral-1-one, exemplified by compound **XXIII-1**, which is prepared according to the methods described in M. J. Fisher *et al.* (EP 0635492, Jan. 25,

1995), is treated with triflic anhydride to provide the triflate, as exemplified by compound **XXIII -2**, which is employed in a palladium catalyzed carbonylation reaction to afford a carboxylic acid, such as compound **XXIII -3**, which is then condensed with an amine to provide, after deesterification, the 6-aminoacyl compound, **XXIII -5**. Alternatively, the palladium catalyzed carbonylation reaction with the triflate exemplified by compound **XXIII -2**, may be trapped with said amine compound to provide, after saponification, the corresponding 6-aminoacyl compound, **XXIII -5**.

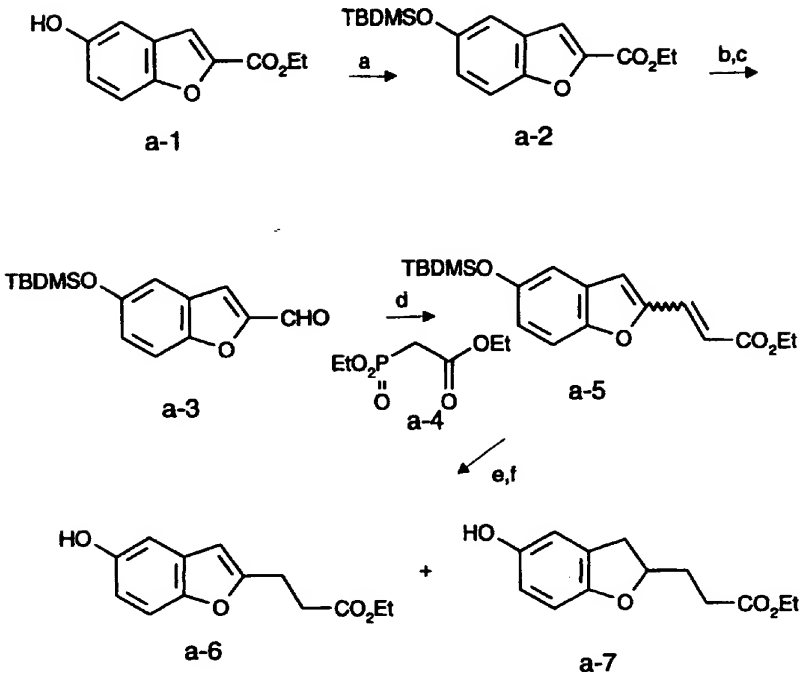
Scheme XXIV



a) $BrCH_2CO_2Et$, K_2CO_3, NaI; b) 1. DBU, EtOH, 2. HCl, EtOH; c) DiBAL, -78 ° C; d) NaH, THF; e)H_2, 10% Pd-C; f) R_2CO-X; g)1N NaOH, MeOH

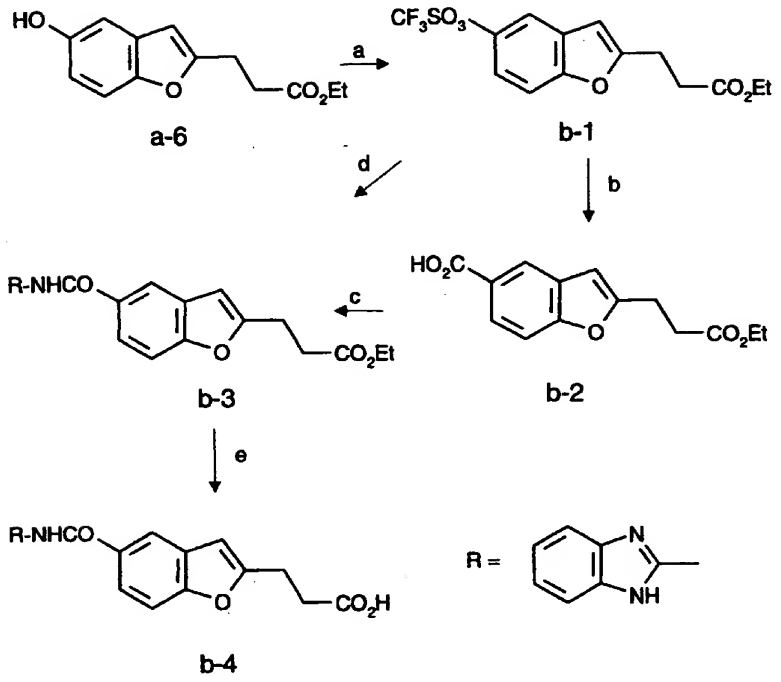
Scheme XXIV provides a method for the preparation of 5-acylaminobenzofuran and 5-acylaminodihydrobenzofuran compounds as exemplary fibrinogen receptor antagonists, as described in M. L. Denney, *et al.* (EP 0655439, 31/5/95). Accordingly, a 4-nitrosalicylaldehyde, exemplified by compound **XXIV-1**, is treated with a haloacetic acid ester to give the phenoxyacetic acid ester, exemplified by compound **XXIV -2**. A 2-alkoxycarbonylfuran, exemplified by compound **XXIV -3**, is obtained by treating the aldehyde with base, for example with DBU. The 2-alkoxycarbonyl group is reduced to the aldehyde, for example with DiBAL. Wittig reaction affords the 2-acrylate ester, exemplified by compound **XXIV -4**, which is reduced to the benzofuran-2-propionic acid ester, exemplified by compound **XXIV -5** and the dihydrobenzofuran-2-propionic acid ester, exemplified by compound **XXIV -6**. The amine **XXIV -5** is then condensed with an activated derivative of a carboxylic acid to provide, after deesterification, the amide 5, **XXIV -8**. Alternatively, the amine **XXIV -6** is condensed with an activated derivative of a carboxylic acid to provide, after deesterification, the amide, **XXIV -7**.

Scheme XXVa



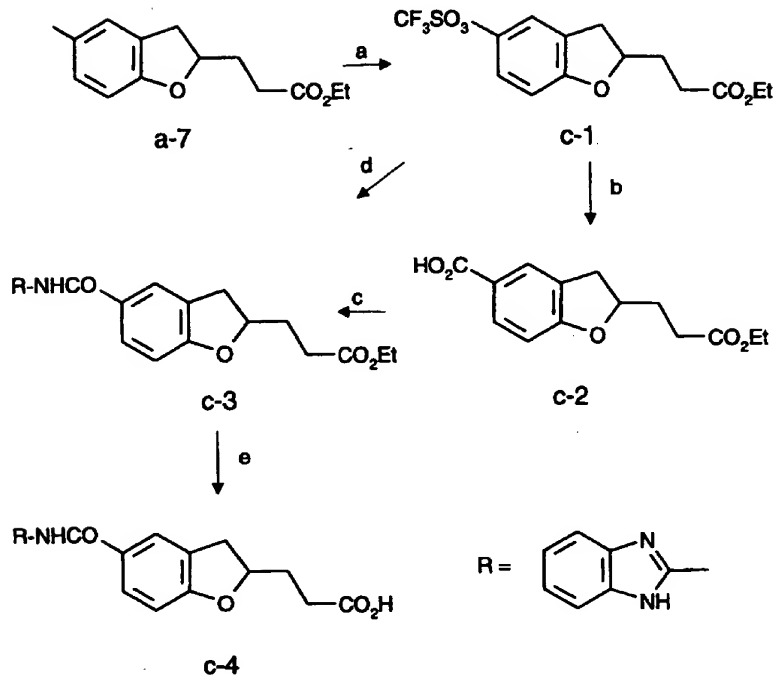
a) 1. TBDMS-Cl, imidazole; b)DiBAl-H, -78 °C, d) NaH, THF; e) H_2, 5% Pd-C; f) $Et_4N+ F-$

Scheme XXVb



a) $(CF_3SO_2)_2O$; b) CO, $Pd(OAc)_2$, PPh_3, DIEA, NMP, NH_4HCO_3, H_2O; c) H_2N-R, EDC / HOBt, DIEA, DMF; d) H_2N-R, CO, $Pd(OAc)_2$, PPh_3, DIEA, NMP, NH_4HCO_3, H2O e) 1N NaOH, EtOH

Scheme XXVc



a) $(CF_3SO_2)_2O$; b) CO, $Pd(OAc)_2$, PPh_3, DIEA, NMP, NH_4HCO_3, H_2O; c) H_2N-R, EDC / HOBt, DIEA, DMF; d) H_2N-R, CO, $Pd(OAc)_2$, PPh_2, DIEA, NMP, NH_4HCO_3, H2O e) 1N NaOH, EtOH

Scheme XXV provides a method for the preparation of 5-aminoacylbenzofuran and 5-aminoacyldihydrobenzofuran compounds as exemplary fibrinogen receptor antagonists, as described in M. L. Denney, *et al.* (EP 0655439, 31/5/95). Accordingly, a 5-hydroxybenzofuran-2-carboxylic acid ester, such as compound **XXVa-1**, prepared in the manner of M. L. Denney, *et al.* (EP 0655439, 31/5/95), is treated with TBDMS-Cl to provide the TBDMS derivative of the ester, **XXVa-2**. The ester is reduced to an aldehyde, such as compound **XXVa-3**. Wittig

reaction affords the acrylic acid ester, **XXVa-4**. Catalytic reduction affords the benzofuran-2-acetic acid ester and the dihydrobenzofuran-2-acetic acid ester. Cleavage of the silyl ether group of each ester, by methods known to the art, affords either the benzofuran-2-acetic acid ester, **XXVa-5**, or the dihydrobenzofuran-2-acetic acid ester, **XXVa-6**.

As seen in Scheme XXVb and XXVc, each alcohol in turn may be converted to a carboxylic acid via palladium catalyzed carbonylation, such as compound **XXVb-2** or **XXVc-2**, which is then condensed with an amine to provide, after deesterification, the amide **XXVb-4** or **XXVc-4**. Alternatively, the palladium catalyzed carbonylation reaction with the triflate exemplified by compound **XXVb-1**, or **XXVc-1**, may be trapped with said aminomethyl compound to provide, after deesterification, the corresponding 6-aminoacyl compound, **XXVb-4** or **XXVc-4**.

Amide coupling reagents as used herein denote reagents which may be used to form peptide bonds. Typical coupling methods employ carbodiimides, activated anhydrides and esters and acyl halides. Reagents such as EDC, DCC, DPPA, PPA, BOP reagent, HOBt, N-hydroxysuccinimide and oxalyl chloride are typical.

Coupling methods to form peptide bonds are generally well known to the art. The methods of peptide synthesis generally set forth by Bodansky *et al.*, THE PRACTICE OF PEPTIDE SYNTHESIS, Springer-Verlag, Berlin, 1984, Ali *et al.* in *J. Med. Chem.*, 29, 984 (1986) and *J. Med. Chem.*, 30, 2291 (1987) are generally illustrative of the technique and are incorporated herein by reference.

Typically, the amine or aniline is coupled via its free amino group to an appropriate carboxylic acid substrate using a suitable carbodiimide coupling agent, such as N,N' dicyclohexyl carbodiimide (DCC), optionally in the presence of catalysts such as 1-hydroxybenzotriazole (HOBt) and dimethylamino pyridine (DMAP). Other methods, such as the formation of activated esters, anhydrides or acid halides, of the free carboxyl of a suitably protected acid substrate, and subsequent reaction with the free amine of a suitably protected amine, optionally in the presence of a base, are also suitable. For example, a protected Boc-amino acid or

Cbz-amidino benzoic acid is treated in an anhydrous solvent, such as methylene chloride or tetrahydrofuran(THF), in the presence of a base, such as N-methyl morpholine, DMAP or a trialkylamine, with isobutyl chloroformate to form the "activated anhydride", which is subsequently reacted with the free amine of a second protected amino acid or aniline.

The compounds of formula (XIX) and (XX) are commercially available or are prepared by methods known in the art such as illustrated herein disclosed in standard reference books, like the COMPENDIUM OF ORGANIC SYNTHETIC METHODS, Vol. I-VI (Wiley-Interscience). A generally applicable route to benzimidazoles is disclosed in Nestor et al, *J. Med. Chem.* **1984**, *27*, 320. Representative methods for preparing compounds of formula (XX) are also common to the art and may be found, for instance, in EP-A 0 381 033.

Acid addition salts of the compounds are prepared in a standard manner in a suitable solvent from the parent compound and an excess of an acid, such as hydrochloric, hydrobromic, hydrofluoric, sulfuric, phosphoric, acetic, trifluoroacetic, maleic, succinic or methanesulfonic. Certain of the compounds form inner salts or zwitterions which may be acceptable. Cationic salts are prepared by treating the parent compound with an excess of an alkaline reagent, such as a hydroxide, carbonate or alkoxide, containing the appropriate cation; or with an appropriate organic amine. Cations such as Li^+, Na^+, K^+, Ca^{++}, Mg^{++} and NH_4^+ are specific examples of cations present in pharmaceutically acceptable salts.

This invention also provides a pharmaceutical composition which comprises a compound according to formula (I)-(V) and (XXI)-(XXII) and a pharmaceutically acceptable carrier. Accordingly, the compounds of formula (I)-(V) and (XXI)-(XXII) may be used in the manufacture of a medicament. Pharmaceutical compositions of the compounds of formula (I)-(V) and (XXI)-(XXII) prepared as hereinbefore described may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or

buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, these compounds may be encapsulated, tableted or prepared in a emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Liquid carriers include syrup, peanut oil, olive oil, saline and water. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

For rectal administration, the compounds of this invention may also be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository.

The compounds described herein are antagonists of the vitronectin receptor, and are useful for treating diseases wherein the underlying pathology is attributable to ligand or cell which interacts with the vitronectin receptor. For instance, these compounds are useful for the treatment of diseases wherein loss of the bone matrix creates pathology. Thus, the instant compounds are useful for the treatment of ostoeporosis, hyperparathyroidism, Paget's disease, hypercalcemia of malignancy, osteolytic lesions produced by bone metastasis, bone loss due to immobilization or sex hormone deficiency. The compounds of this invention are also believed to have

utility as antitumor, anti-angiogenic, antiinflammatory and anti-metastatic agents, and be useful in the treatment of atherosclerosis and restenosis.

The compound is administered either orally or parenterally to the patient, in a manner such that the concentration of drug is sufficient to inhibit bone resorption, or other such indication. The pharmaceutical composition containing the peptide is administered at an oral dose of between about 0.1 to about 50 mg/kg in a manner consistent with the condition of the patient. Preferably the oral dose would be about 0.5 to about 20 mg/kg. For acute therapy, parenteral administration is preferred. An intravenous infusion of the peptide in 5% dextrose in water or normal saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. Typically, the parenteral dose will be about 0.01 to about 100 mg/kg; preferably between 0.1 and 20 mg/kg. The compounds are administered one to four times daily at a level to achieve a total daily dose of about 0.4 to about 400 mg/kg/day. The precise level and method by which the compounds are administered is readily determined by one routinely skilled in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect.

The compounds may be tested in one of several biological assays to determine the concentration of compound which is required to have a given pharmacological effect.

Inhibition of vitronectin binding

Solid-Phase [^{3}H]-SK&F-107260 Binding to $\alpha_v\beta_3$: Human placenta or human platelet $\alpha_v\beta_3$ (0.1-0.3 mg/mL) in buffer T (containing 2 mM $CaCl_2$ and 1% octylglucoside) was diluted with buffer T containing 1 mM $CaCl_2$, 1 mM $MnCl_2$, 1 mM $MgCl_2$ (buffer A) and 0.05% NaN_3, and then immediately added to 96-well ELISA plates (Corning, New York, NY) at 0.1 mL per well. 0.1 - 0.2 µg of $\alpha_v\beta_3$ was added per well. The plates were incubated overnight at 4°C. At the time of the experiment, the wells were washed once with buffer A and were incubated with 0.1 mL of 3.5% bovine serum albumin in the same buffer for 1 hr at room

temperature. Following incubation the wells were aspirated completely and washed twice with 0.2 mL buffer A.

Compounds were dissolved in 100% DMSO to give a 2 mM stock solution, which was diluted with binding buffer (15 mM Tris-HCl (pH 7.4), 100 mM NaCl, 1 mM $CaCl_2$, 1 mM $MnCl_2$, 1 mM $MgCl_2$) to a final compound concentration of 100 μM. This solution is then diluted to the required final compound concentration. Various concentrations of unlabeled antagonists (0.001 - 100 μM) were added to the wells in triplicates, followed by the addition of 5.0 nM of [^{3}H]-SK&F-107260 (65 - 86 Ci/mmol).

The plates were incubated for 1 hr at room temperature. Following incubation the wells were aspirated completely and washed once with 0.2 mL of ice cold buffer A in a well-to-well fashion. The receptors were solubilized with 0.1 mL of 1% SDS and the bound [^{3}H]-SK&F-107260 was determined by liquid scintillation counting with the addition of 3 mL Ready Safe in a Beckman LS Liquid Scintillation Counter, with 40% efficiency. Nonspecific binding of [^{3}H]-SK&F-107260 was determined in the presence of 2 μM SK&F-107260 and was consistently less than 1% of total radioligand input. The IC_{50} (concentration of the antagonist to inhibit 50% binding of [^{3}H]-SK&F-107260) was determined by a nonlinear, least squares curve-fitting routine, which was modified from the LUNDON-2 program. The K_i (dissociation constant of the antagonist) was calculated according to the equation: $K_i = IC_{50}/(1 + L/K_d)$, where L and K_d were the concentration and the dissociation constant of [^{3}H]-SK&F-107260, respectively.

Compounds of the present invention inhibit vitronectin binding to SK&F 107260 in the concentration range of about 0.001 to 50 micromolar.

Compounds of this invention are also tested for *in vitro* and *in vivo* bone resorption in assays standard in the art for evaluating inhibition of bone formation, such as the pit formation assay disclosed in EP 528 587, which may also be performed using human osteoclasts in place of rat osteoclasts, and the ovarectomized rat model, described by Wronski *et al.*, *Cells and Materials* **1991**, Sup. 1, 69-74.

Vascular smooth muscle cell migration assay

Rat or human aortic smooth muscle cells were used. The cell migration was monitored in a Transwell cell culture chamber by using a polycarbonate membrane with pores of 8 um (Costar). The lower surface of the filter was coated with vitronectin. Cells were suspended in DMEM supplemented with 0.2% bovine serum albumin at a concentration of 2.5 - 5.0 x 10^6 cells/mL, and were pretreated with test compound at various concentrations for 20 min at 20°C. The solvent alone was used as control. 0.2 mL of the cell suspension was placed in the upper compartment of the chamber. The lower compartment contained 0.6 mL of DMEM supplemented with 0.2% bovine serum albumin. Incubation was carried out at 37°C in an atmosphere of 95% air/5% CO_2 for 24 hr. After incubation, the non-migrated cells on the upper surface of the filter were removed by gentle scraping. The filter was then fixed in methanol and stained with 10% Giemsa stain. Migration was measured either by a) counting the number of cells that had migrated to the lower surface of the filter or by b) extracting the stained cells with 10% acetic acid followed by determining the absorbance at 600 nM.

PARATHYROIDECTOMIZED RAT MODEL

Each experimental group consists of 5-6 male Sprague-Dawley rats. The rats are parathyroidectomized (by the vendor, Taconic Farms) 7 days prior to use. Twenty four hours prior to use, circulating ionized calcium levels are measured in whole blood immediately after it has been withdrawn by tail venipuncture into heparinized tubes. Rats are included if ionized Ca level (measured with a Ciba-Corning model 634 calcium pH analyzer) is _1.2 mM/L. The rats are then put on a diet of calcium-free chow and deionized water. At the start of the experiment the rats weigh approximately 100g. Baseline Ca levels are measured and the rats are administered control vehicle (saline) or compound (dissolved in saline) as a single intravenous (tail vein) bolus injection followed immediately by a single subcutaneous injection of either human parathyroid hormone 1-34 peptide (hPTH1-34, dose 0.2mg/kg in saline/0.1% bovine serum albumen, Bachem, Ca)

or the PTH vehicle. The calcemic response to PTH (and any effect of compound on this response) is measured 2h after compound/PTH administration.

RAT ULNA DRIFT MODEL

Each experimental group consists of 8-10 male Sprague-Dawley or Wistar rats of approximately 30-40g body weight at the start of the experiment. The agent being tested is administered by an appropriate route as single or multiple daily doses for a period of seven days. Prior to administration of the first dose, the rats are given a single dose of a fluorescent marker (tetracycline 25mg/kg, or calcein 10mg/kg) that labels the position of bone forming surfaces at that point in time. After dosing of compound has been completed, the rats are killed and both forelimbs are removed at the elbow, the foot is removed at the ankle and the skin removed. The sample is frozen and mounted vertically on a microtome chuck. Cross sections of the midshaft region of the ulna are cut in the cryostat. The rate of bone resorption is measured morphometrically in the medial-dorsal portion of the cortical bone. The measurement is done as follows: the amount of bone resorbed at the periosteal surface is equal to the distance by which the periosteal surface has advanced towards the fluorescent label which had been incorporated at the endosteal bone formation surface on day zero; this distance is calculated by subtracting the width of bone between the label and the periosteal surface on day 7 from the width on day zero; the resorption rate in microns per day is calculated by dividing the result by 7.

HUMAN OSTEOCLAST RESORPTION ASSAY ("PIT ASSAY")

- Aliquots of osteoclastoma-derived cell suspensions are removed from liquid nitrogen strorage, warmed rapidly at 37°C and washed x1 in RPMI-1640 medium by centrifugation (1000rpm, 5 mins at 4°C).

- Aspirate the medium and replace it with murine anti-HLA-DR antibody, diluted 1:3 in RPMI-1640 medium. Incubate for 30 mins on ice and mix the cell suspension frequently.

• The cells are washed x2 with cold RPMI-1640 by centrifugation (1000 rpm, 5 mins at 4°C) and the cells are transferred to a sterile 15 ml centrifuge tube. The number of mononuclear cells are enumerated in an improved Neubauer counting chamber.

• Sufficient magnetic beads (5 / mononuclear cell), coated with goat anti-mouse IgG, are removed from their stock bottle and placed into 5 ml of fresh medium (this washes away the toxic azide preservative). The medium is removed by immobilizing the beads on a magnet and is replaced with fresh medium.

• The beads are mixed with the cells and the suspension is incubated for 30 mins on ice. The suspension is mixed frequently.

• The bead-coated cells are immobilized on a magnet and the remaining cells (osteoclast-rich fraction) are decanted into a sterile 50 ml centrifuge tube.

• Fresh medium is added to the bead-coated cells to dislodge any trapped osteoclasts. This wash process is repeated x10. The bead-coated cells are discarded.

• The osteoclasts are enumerated in a counting chamber, using a large-bore disposable plastic pasteur to charge the chamber with the sample.

• The cells are pelleted by centrifugation and the density of osteoclasts adjusted to $1.5x10^4$/ml in EMEM medium, supplemented with 10% fetal calf serum and 1.7g/litre of sodium bicarbonate.

• 3ml aliquots of the cell suspension (per treatment) are decanted into 15ml centrifuge tubes. The cells are pelleted by centrifugation.

• To each tube 3ml of the appropriate treatment are added (diluted to 50 uM in the EMEM medium). Also included are appropriate vehicle controls, a positive control

(87MEM1 diluted to 100 ug/ml) and an isotype control (IgG2a diluted to 100 ug/ml). Incubate at 37°C for 30 mins.

• 0.5ml aliquots of the cells are seeded onto sterile dentine slices in a 48-well plate and incubated at 37°C for 2 hours. Each treatment is screened in quadruplicate.

• The slices are washed in six changes of warm PBS (10 ml / well in a 6-well plate) and then placed into fresh treatment or control. Incubate at 37°C for 48 hours.

Tartrate resistant acid phosphatase (TRAP) procedure (selective stain for cells of the osteoclast lineage).

• The slices are washed in phosphate buffered saline and fixed in 2% gluteraldehyde (in 0.2M sodium cacodylate) for 5 mins.

• They are washed in water and incubated in TRAP buffer for 5 mins at 37°C.

• Following a wash in cold water they are incubated in cold acetate buffer / fast red garnet for 5 mins at 4°C.

• Excess buffer is aspirated, and the slices are air dried following a wash in water.

• The TRAP positive osteoclasts are enumerated by bright-field microscopy and are then removed from the surface of the dentine by sonication.

• Pit volumes are determined using the Nikon/Lasertec ILM21W confocal microscope.

Human osteoclast resorption and adhesion assays

Pit resorption and adhesion assays have been developed and standardized using normal human osteoclasts derived from osteoclastoma tissue. The osteoclast

population is negatively selected from the osteoclastoma cell suspensions using magnetic beads (Dynal Inc, NY). These beads are coated with a murine monoclonal antibody that recognizes a human class II major histocompatibility antigen that is present on a large number of mononuclear cells in the cell suspensions. The cells that express this antigen, and consequently bind the beads, are removed from the mixture of cells using a magnet. The osteoclast-rich suspension is then ready to use in the assays detailed below.

Resorption assay (with ELISA readout)

Enriched preparations of osteoclasts are preincubated for 30 minutes at 37°C with test compound (4 doses) or controls. They are then seeded onto bovine cortical bone slices in wells of a 48-well tissue culture plate and are incubated for a further 2 hours at 37°C. The bone slices are washed in six changes of warm phosphate buffered saline (PBS), to remove non-adherent cells, and are then returned to wells of a 48 well plate containing fresh compound or controls. The tissue culture plate is then incubated for 48 hours at 37°C. The supernatants from each well are aspirated into individual tubes and are screened in a competitive ELISA that detects a collagen peptide that is released during the resorption process. This is a commercially available ELISA (Osteometer, Denmark) that contains a rabbit antibody that specifically reacts with an 8-amino acid sequence (Glu-Lys-Ala-His- Asp-Gly-Gly-Arg) that is present in the carboxy-terminal telopeptide of the α1-chain of type I collagen. The results are expressed as % inhibition of resorption compared to a vehicle control.

Adhesion assay

Osteoclastoma-derived osteoclasts are preincubated with compound (4 doses) or controls at 37°C for 30 minutes. The cells are then seeded onto osteopontin-coated slides (human or rat osteopontin, 2.5ug/ml) and incubated for 2 hours at 37°C. Non adherent cells are removed by washing the slides vigorously in PBS and the cells remaining on the slides are fixed in acetone. The osteoclasts are stained for tartrate-resistant acid phosphatase (TRAP), a selective marker for cells of this phenotype, and are enumerated by light microscopy. The results are expressed as % inhibition of adhesion compared to a vehicle control.

Inhibition of RGD-mediated GPIIb-IIIa binding

Purification of GPIIb-IIIa

Ten units of outdated, washed human platelets (obtained from Red Cross) were lyzed by gentle stirring in 3% octylglucoside, 20 mM Tris-HCl, pH 7.4, 140 mM NaCl, 2 mM $CaCl_2$ at 4°C for 2 h. The lysate was centrifuged at 100,000g for 1 h. The supernatant obtained was applied to a 5 mL lentil lectin sepharose 4B column (E.Y. Labs) preequilibrated with 20 mM Tris-HCl, pH 7.4, 100 mM NaCl, 2 mM $CaCl_2$, 1% octylglucoside (buffer A). After 2 h incubation, the column was washed with 50 mL cold buffer A. The lectin-retained GPIIb-IIIa was eluted with buffer A containing 10% dextrose. All procedures were performed at 4°C. The GPIIb-IIIa obtained was >95% pure as shown by SDS polyacrylamide gel electrophoresis.

Incorporation of GPIIb-IIIa in Liposomes.

A mixture of phosphatidylserine (70%) and phosphatidylcholine (30%) (Avanti Polar Lipids) were dried to the walls of a glass tube under a stream of nitrogen. Purified GPIIb-IIIa was diluted to a final concentration of 0.5 mg/mL and mixed with the phospholipids in a protein:phospholipid ratio of 1:3 (w:w). The mixture was resuspended and sonicated in a bath sonicator for 5 min. The mixture was then dialyzed overnight using 12,000-14,000 molecular weight cutoff dialysis tubing against a 1000-fold excess of 50 mM Tris-HCl, pH 7.4, 100 mM NaCl, 2 mM CaCl2 (with 2 changes). The GPIIb-IIIa-containing liposomes wee centrifuged at 12,000g for 15 min and resuspended in the dialysis buffer at a final protein concentration of approximately 1 mg/mL. The liposomes were stored at -70C until needed.

Competitive Binding to GPIIb-IIIa

The binding to the fibrinogen receptor (GPIIb-IIIa) was assayed by an indirect competitive binding method using [^{3}H]-SK&F-107260 as an RGD-type ligand. The binding assay was performed in a 96-well filtration plate assembly (Millipore Corporation, Bedford, MA) using 0.22 um hydrophilic durapore membranes. The wells were precoated with 0.2 mL of 10 µg/mL polylysine (Sigma Chemical Co., St. Louis, MO.) at room temperature for 1 h to block nonspecific binding. Various concentrations of unlabeled benzadiazapines were added to the

wells in quadruplicate. [^{3}H]-SK&F-107260 was applied to each well at a final concentration of 4.5 nM, followed by the addition of 1 μg of the purified platelet GPIIb-IIIa-containing liposomes. The mixtures were incubated for 1 h at room temperature. The GPIIb-IIIa-bound [3H]-SK&F-107260 was seperated from the unbound by filtration using a Millipore filtration manifold, followed by washing with ice-cold buffer (2 times, each 0.2 mL). Bound radioactivity remaining on the filters was counted in 1.5 mL Ready Solve (Beckman Instruments, Fullerton, CA) in a Beckman Liquid Scintillation Counter (Model LS6800), with 40% efficiency. Nonspecific binding was determined in the presence of 2 μM unlabeled SK&F-107260 and was consistently less than 0.14% of the total radioactivity added to the samples. All data points are the mean of quadruplicate determinations.

Competition binding data were analyzed by a nonlinear least-squares curve fitting procedure. This method provides the IC50 of the antagonists (concentration of the antagonist which inhibits specific binding of [^{3}H]-SK&F-107260 by 50% at equilibrium). The IC50 is related to the equilibrium dissociation constant (Ki) of the antagonist based on the Cheng and Prusoff equation: Ki = IC50/(1+L/Kd), where L is the concentration of [3H]-SK&F-107260 used in the competitive binding assay (4.5 nM), and Kd is the dissociation constant of [3H]-SK&F-107260 which is 4.5 nM as determined by Scatchard analysis

Compounds of the present invention inhibit the vitronectin binding to SK&F 007260 with a Ki at the vitronectin receptor that is about ten-fold greater than that for the fibrinogen receptor. Preferred compounds have a Ki at the vitronectin receptor that is thirty-fold greater than that at the fibrinogen receptor. The most preferred compounds have a Ki at the vitronectin receptor that is a hundred-fold greater than that at the fibrinogen receptor.

The examples which follow are intended in no way to limit the scope of this invention, but are provided to illustrate how to make and use the compounds of this invention. Many other embodiments will be readily apparent to those skilled in the art.

General

Nuclear magnetic resonance spectra were recorded at either 250 or 400 MHz using, respectively, a Bruker AM 250 or Bruker AC 400 spectrometer. $CDCl_3$ is deuteriochloroform, DMSO-d_6 is hexadeuteriodimethylsulfoxide, and CD_3OD is tetradeuteriomethanol. Chemical shifts are reported in parts per million (δ) downfield from the internal standard tetramethylsilane. Abbreviations for NMR data are as follows: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets, dt=doublet of triplets, app=apparent, br=broad. J indicates the NMR coupling constant measured in Hertz. Continuous wave infrared (IR) spectra were recorded on a Perkin-Elmer 683 infrared spectrometer, and Fourier transform infrared (FTIR) spectra were recorded on a Nicolet Impact 400 D infrared spectrometer. IR and FTIR spectra were recorded in transmission mode, and band positions are reported in inverse wavenumbers (cm^{-1}). Mass spectra were taken on either VG 70 FE, PE Syx API III, or VG ZAB HF instruments, using fast atom bombardment (FAB) or electrospray (ES) ionization techniques. Elemental analyses were obtained using a Perkin-Elmer 240C elemental analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. All temperatures are reported in degrees Celsius.

Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Both flash and gravity chromatography were carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel. Analytical and preparative HPLC were carried out on Rainin or Beckman chromatographs. ODS refers to an octadecylsilyl derivatized silica gel chromatographic support. 5 μ Apex-ODS indicates an octadecylsilyl derivatized silica gel chromatographic support having a nominal particle size of 5 μ, made by Jones Chromatography, Littleton, Colorado. YMC ODS-AQ® is an ODS chromatographic support and is a registered trademark of YMC Co. Ltd., Kyoto, Japan. PRP-1® is a polymeric (styrene-divinylbenzene) chromatographic support, and is a registered trademark of Hamilton Co., Reno, Nevada) Celite® is a filter aid composed of acid-washed diatomaceous silica, and is a registered trademark of Manville Corp., Denver, Colorado.

Methyl (±)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate, methyl (2S)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate, methyl (2R)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate, methyl (±)-7-carboxy-4-

isopropyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate, methyl (±)-7-carboxy-3-oxo-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate, methyl (±)-8-carboxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, methyl (±) 7-amino-5-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid, and tert-butyl 4-fluoro-3-methylbenzoate were prepared by the method of Bondinell, et al., WO 93/00095. Methyl (±)-7-carboxy-4-(2-methoxyethyl)-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate, methyl (±)-7-carboxy-4-[2-(3,4-methylenedioxyphenyl)ethyl]-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate,methyl (±)-7-carboxy-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate, methyl (±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate, (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid, 2-(methylaminomethyl)benzimidazole dihydrochloride, and 4-aza-5-methyl-2-(methylamino)methylbenzimidazole were prepared according to P50256-1.

Preparation 1

Preparation of 2-(aminomethyl)-4-aza-5-methylbenzimidazole dihydrochloride

a) 2,3-Diamino-6-methylpyridine

10% Pd/C (3.2 g, 3 mmole) was added to a solution of 2-Amino-6-methyl-3-nitropyridine (2.30 g, 15 mmole) in absolute EtOH (150 mL), and the mixture was shaken at RT under H_2 (50 psi). After 1.5 hr, the mixture was filtered through celite®, and the filtrate was concentrated under vacuum to afford the title compound as a yellow oil. This was used without further purification: ^{1}H NMR (250 MHz, CD_3OD) δ 6.82 (d, 1H), 6.36 (d, 1H), 2.25 (s, 3H).

b) 2-Amino-3-[(benzyloxycarbonyl)glycyl]amino-6-methylpyridine

DCC (3.09 g, 15 mmole) was added to a solution of 2,3-diamino-6-methylpyridine (15 mmole) and Cbz-glycine (3.14 g, 15 mmole) in DMF (19 mL) and CH_2Cl_2 (19 mL) at 0°C under argon. When the DCC had dissolved, the slightly cloudy solution was warmed to RT. After 18.5 hr, the mixture was filtered through celite®, and the filtrate was concentrated to dryness on the rotavap. The residue was reconcentrated from xylenes (to remove DMF) to leave a yellow solid. Silica gel chromatography (10% MeOH/$CHCl_3$) gave the title compound (2.24 g, 48%) as a yellow solid: TLC R_f (10% MeOH/$CHCl_3$) 0.57; ^{1}H NMR (250 MHz, DMSO - d_6) δ

9.11 (br s, 1 H), 7.48 - 7.60 (br t, 1 H), 7.20 - 7.48 (m, 6 H), 6.40 (d, 1 H), 5.69 (br s, 2 H), 5.06 (s, 2 H), 3.82 (d, 2 H), 2.23 (s, 3 H).

c) 4-Aza-2-(benzyloxycarbonyl)aminomethyl-5-methylbenzimidazole

A solution of 2-amino-3-[(benzyloxycarbonyl)glycyl]amino-6-methylpyridine (2.24 g, 7.13 mmole) in glacial AcOH (70 mL) was heated to reflux under argon. After 17 hr, the solution was concentrated (rotavap, high vacuum), and the residue was reconcentrated from toluene (to remove AcOH). The resulting yellow oil was treated with hot EtOAc (20 mL) and the mixture was cooled to RT. The solid was collected by suction filtration and washed with EtOAc to afford the title compound (1.72 g, 81%) as an off-white solid: TLC R_f (15% MeOH/$CHCl_3$) 0.63; MS (ES) m/e 297.4 $(M + H)^+$.

d) 2-(Aminomethyl)-4-aza-5-methylbenzimidazole dihydrochloride

10% Pd/C (153 mg, 0.14 mmole) was added to a solution of 4-aza-2-(benzyloxycarbonyl)aminomethyl-5-methylbenzimidazole (213.4 mg, 0.72 mmole) and 1.0 N HCl (1.44 mL, 1.44 mmole) in absolute EtOH (7.2 mL). The mixture was purged with H_2, then was stirred briskly at RT under H_2 (balloon). After 2 hr, the reaction was filtered through celite, and the filtrate was concentrated on the rotavap to leave the title compound as an off-white solid: MS (ES) m/e 163.2 $(M + H)^+$.

Preparation 2

Preparation of methyl (±)-2,3,4,5-tetrahydro-7-carboxy-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetate

a) tert-Butyl 3-[(3,3-dimethylbutyl)amino]methyl-4-nitrobenzoate

A mixture of tert-butyl 3-methyl-4-nitrobenzoate (WO 93/00095; 17.7 g, 74.7 mmol), NBS (19.9 g, 112.0 mmol), benzoyl peroxide (1.81 g, 7.47 mmol), and CCl_4 (370 mL) was heated at reflux. After 17.5 h, the reaction was cooled thoroughly in ice and filtered to remove the precipitated succinimide. The filtrate was concentrated to leave a brownish-yellow oil.

This oil (4.2 g, 13.29 mmol), was dissolved in dry THF (50 mL), and 3,3-dimethylbutylamine (3.0 g, 29.64 mmol) was added all at once. The orangish-yellow solution was stirred at RT for 80 min, then was concentrated to remove the THF. The residue was diluted with Et_2O (150 mL) and washed sequentially with 1.0 N NaOH (25 mL) and H_2O (25 mL). The combined aqueous layers were back-

extracted with Et_2O (50 mL), and the combined organic layers were washed with brine (25 mL) and dried ($MgSO_4$). Concentration gave the crude title compound (4.19 g, 94%) as a light-brown oil: MS (ES) m/e 337.2 $(M+H)^+$.

b) tert-Butyl 3-[[N-(3,3-dimethylbutyl)-N-(tert-butoxycarbonyl)]amino]methyl-4-nitrobenzoate

Di-tert-butyl dicarbonate (4.0 g, 18.39 mmol) was added all at once to a solution of tert-butyl 3-[(3,3-dimethylbutyl)amino]methyl-4-nitrobenzoate (4.12 g, 12.26 mmol) in $CHCl_3$ (80 mL) at RT. After 18 h, the reaction was concentrated and reconcentrated from hexanes (to remove $CHCl_3$). Silica gel chromatography (10-25% EtOAc/hexanes) gave the title compound (5.0 g, 93%) as a yellow oil: MS (ES) m/e 437.2 $(M+H)^+$, 459.2 $(M+Na)^+$.

c) tert-Butyl 4-amino-3-[[N-(3,3-dimethylbutyl)-N-(tert-butoxycarbonyl)]amino]methyl benzoate

10% Pd/C (1.0 g, 0.94 mmol) was added to a solution of tert-butyl 3-[[N-(3,3-dimethylbutyl)-N-(tert-butoxycarbonyl)]amino]methyl-4-nitrobenzoate (4.95 g, 11.35 mmol) in EtOAc (50 mL), and the mixture was shaken on a Parr apparatus at RT under H_2 (55 psi). After 4 h, the reaction was filtered through celite®, and the filtrate was concentrated to afford the title compound (4.3 g, 93%) as a reddish-brown oil: MS (ES) m/e 407.4 $(M+H)^+$.

d) tert-Butyl (±)-4-[2-(1,4-dimethoxy-1,4-dioxobutyl)amino]-3-[[N-(3,3-dimethylbutyl)-N-(tert-butoxycarbonyl)]amino]methylbenzoate

A solution of tert-butyl 4-amino-3-[[N-(3,3-dimethylbutyl)-N-(tert-butoxycarbonyl)]amino]methylbenzoate (5.6 g, 13.79 mmol) and dimethylacetylene dicarboxylate (1.86 mL, 15.17 mmol) in MeOH (28 mL) was heated at reflux for 1 h, then was cooled to RT. The resulting solution was combined with MeOH (80 mL) and 10% Pd/C (2.9 g, 2.76 mmol), and the mixture was shaken on a Parr apparatus at RT under H_2 (50 psi). After 22 h, the reaction was filtered through celite®, and the filtrate was concentrated on the rotavap. The residue was reconcentrated from $CHCl_3$ (to remove MeOH), then was chromatographed on silica gel (25% EtOAc/hexanes). The title compound (2.64 g, 42%) was obtained as a faintly yellow oil: MS (ES) m/e 551.2 $(M+H)^+$.

e) Methyl (±)-2,3,4,5-tetrahydro-7-carboxy-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

TFA (25 mL) was added all at once to a solution of tert-butyl (±)-4-[2-(1,4-dimethoxy-1,4-dioxobutyl)amino]-3-[[N-(3,3-dimethylbutyl)-N-(tert-butoxycarbonyl)]amino]methylbenzoate (12.64 g, 4.8 mmol) in anhydrous CH_2Cl_2 (25 mL) at 0°C, and the faintly yellow solution was warmed to RT. After 1 h, the solution was concentrated on the rotavap, and the residue was reconcentrated from toluene (to remove residual TFA). The resulting oil was combined with toluene (50 mL) and Et_3N (3.34 mL, 24 mmol), and the mixture was heated to reflux. A light yellow, homogeneous solution was produced. After 16 h, the reaction was concentrated on the rotavap to leave a solid residue. This was dissolved in a minimum of MeOH (ca. 10 mL), diluted with H_2O (10 mL), and acidified with glacial AcOH to pH 4.5. The mixture was filtered, and the precipitate was washed sequentially with MeOH and Et_2O, then was dried in high vacuum to afford the title compound (1.88 g, 93%) as a nearly colorless powder: MS (ES) m/e 363.2 $(M+H)^+$.

Preparation 3

Preparation of Bis[(benzimidazol-2-yl)methyl]amine tris(trifluoroacetate)

a) Bis[[1-N-(tert-butoxycarbonyl)benzimidazol-2-yl]methyl]-N-(tert-butoxycarbonyl)amine

To a stirred solution of 2-aminomethylbenzimidazole dihydrochloride hydrate (6.26 g, 28.4 mmol) and triethylamine (4.0 mL, 28.4 mmol) in dry THF (50 mL) was added 1-(tert-butoxycarbonyl)-2-(bromomethyl)benzimidazole (P50256-1; 2.00 g, 9.48 mmol) in THF (30 mL),. After 8 h, a solution of di-tert-butyl dicarbonate (10.0 g, 45.84 mmol) in $CHCl_3$ (50 mL) was added slowly. The resulting mixture was stirred at RT overnight then was concentrated. The residue was taken up in CH_2Cl_2 (150 mL), and washed sequentially with water (60 mL), 5% $NaHCO_3$ (60 mL), and brine (60 mL). Drying ($MgSO_4$), concentration, and silica gel chromatography (6% MeOH/CH_2Cl_2) gave the title compound (0.46 g, 8%) as a faint yellow oil: MS (ES) m/e 578.4 $(M+H)^+$.

b) Bis[(benzimidazol-2-yl)methyl]amine tris(trifluoroacetate)

A solution of TFA (3 mL) and CH_2Cl_2 (9 mL) at RT was added all at once to bis[[1-N-(tert-butoxycarbonyl)benzimidazol-2-yl]methyl]-N-(tert-butoxycarbonyl)amine (0.23 g, 0.4 mmol). After 35 min, the solution was concentrated on the rotavap, and the residue was reconcentrated from toluene (to

remove residual TFA) to afford the title compound (0.17 g, 68%) as an off-white powder: MS (ES) m/e 278.0 $(M+H)^+$.

Preparation 4

Preparation of 2-[[1-[(benzimidazol-2-yl)methyl]benzimidazole]methyl]amine bis(trifluoroacetate)

a) [[1-N-(tert-Butoxycarbonyl)benzimidazol-2-yl]methyl]-N-(tert-butoxycarbonyl)amine

To a stirred solution of 2-aminomethylbenzimidazole dihydrochloride hydrate (3.0 g, 13.63 mmol) and triethylamine (8.44 mL, 61.3 mmol) in dry CH_2Cl_2 (50 mL) a solution of di-tert-butyl dicarbonate (6.54 g, 30.0 mmol) in CH_2Cl_2 (50 mL) was added at 0°C. The reaction was stirred at RT for 1 h, then more of triethylamine (1.9 mL, 13.8 mmol) and di-tert-butyl dicarbonate (2.97 g, 13.63 mmol) were added. The resulting mixture was stirred at RT for 24 h, then was concentrated. The residue was taken up in CH_2Cl_2 (50 mL) and washed sequentially with 0.5 N HCl (2x40 mL), 5% NaHCO3 (50 mL), and brine (50 mL). The crude product was recrystallized from CH_2Cl_2/ether to give the title compound (2.8 g, 59%) as a white powder: MS (ES) m/e 348.2 $(M+H)^+$.

b) 2-[[1-[[(1-(tert-Butoxycarbonyl)benzimidazol-2-yl]methyl]benzimidazole]methyl]-N,N-di-(tert-butoxycarbonyl)amine

To a stirred solution of [[1-N-(tert-butoxycarbonyl)benzimidazol-2-yl]methyl]-N-(di-tert-butoxycarbonyl)amine (0.6 g, 1.73 mmol) and NaH (0.1 g, 4.17 mmol) in dry THF (12 mL) and DMF (4 mL) was added 1-(tert-butoxycarbonyl)-2-(bromomethyl)benzimidazole (0.6 g, 1.93 mmol). The resulting mixture was stirred at RT for 1 h, then was concentrated. The residue was taken up in CH_2Cl_2 (100 mL) and washed sequentially with water (50 mL), 5% $NaHCO_3$ (30 mL), and brine (30 mL). Drying ($MgSO_4$), concentration, and silica gel chromatography (2:3 EtOAc/hexanes) gave the title compound (0.27 g, 27%) as a faint yellow oil: MS (ES) m/e 578.2 $(M+H)^+$.

c) 2-[[1-[(Benzimidazol-2-yl)methyl]benzimidazole]methyl]amine bis(trifluoroacetate)

A solution of TFA/CH_2Cl_2 (30 mL, 25%) at RT was added all at once to 2-[[1-[[(1-N-tert-butoxycarbonyl)benzimidazol-2-yl]methyl]benzimidazole]methyl]-N,N-

di-(tert-butoxycarbonyl)amine (0.25 g, 0.43 mmol). After 25 min, the solution was concentrated on the rotavap, and the crude product was recrystallized from CH_2Cl_2/ether to give the title compound (0.17 g, 63%) as an off-white powder: MS (ES) m/e 278.0 $(M+H)^+$.

Example 1

Preparation of (±)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (±)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetate

EDC (138 mg, 0.72 mmole) was added to a solution of methyl (±)-7-carboxy-4-(2-methoxyethyl)-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (202 mg, 0.60 mmole), 2-(aminomethyl)-4-aza-5-methylbenzimidazole dihydrochloride (0.72 mmole), HOBt · H_2O (97 mg, 0.72 mmole), and diisopropylethylamine (0.84 mL, 4.8 mmole) in anhydrous CH_3CN (3 mL) at RT. After 16 hr, the reaction was concentrated, and the residue was reconcentrated from xylenes/$CHCl_3$. Silica gel chromatography (15% MeOH/$CHCl_3$) gave the title compound (impure): TLC R_f (15% MeOH/$CHCl_3$) 0.55; MS (ES) m/e 481.5 $(M + H)^+$. This was used without further purification.

b) (±)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

A two-phase mixture of methyl (±)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.60 mmole), 1.0 N LiOH (1.8 mL, 1.8 mmole), and THF (4.2 mL) was stirred at RT for 45 min, then was concentrated to remove the THF. The aqueous layer was washed with Et_2O (2 x 2 mL), and the Et_2O layers were discarded. The aqueous layer was diluted with CH_3CN (2 mL) and acidified with TFA (0.23 mL). The resulting solution was concentrated to dryness on the rotavap, and the residue was purified by ODS chromatography (12% CH_3CN/H_2O containing 0.1% TFA (250 mL), then 15% CH_3CN/H_2O containing 0.1% TFA). Concentration and lyophilization gave the title compound (199.5 mg, 50% for two steps) as a light

yellow powder: HPLC (PRP-1®, 15% CH_3CN/H_2O containing 0.1% TFA) K' = 1.4; MS (ES) m/e 467 $(M + H)^+$. Anal. Calcd for $C_{23}H_{26}N_6O_5 \cdot 1.5$ $CF_3CO_2H \cdot 1.33$ H_2O: C, 47.21; H, 4.60; N, 12.70. Found: C, 47.20; H, 4.73; N, 12.79.

Example 2

Preparation of (±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetate

EDC (230 mg, 1.2 mmole) was added to a solution of methyl (±)-7-carboxy-4-(2-methoxyethyl)-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (336.4 mg, 1.0 mmole), 2-(aminomethyl)benzimidazole dihydrochloride hydrate (264 mg, 1.2 mmole), HOBt · H_2O (162 mg, 1.2 mmole), and diisopropylethylamine (0.70 mL, 4.0 mmole) in anhydrous DMF (5 mL) at RT. After 17 hr, the reaction was concentrated, and the residue was reconcentrated from xylenes (2 x) to remove DMF. The residue was diluted with H_2O (3 mL) and extracted with $CHCl_3$ (3 x 5 mL). The combined extracts were treated with MeOH (2 mL) to dissolve a precipitate, then were dried ($MgSO_4$) and concentrated. Reconcentration from xylenes (to remove residual DMF) left a light yellow solid. This was dissolved in MeOH/$CHCl_3$, and the solution was concentrated to leave an oil. Silica gel chromatography (10% MeOH/$CHCl_3$) gave an off-white solid, which was triturated with EtOAc (3 mL) to afford the title compound (397.1 mg, 85%) as a colorless solid: TLC R_f (10% MeOH/$CHCl_3$) 0.46; MS (ES) m/e 466.2 $(M + H)^+$.

b) (±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

1.0 N LiOH (1.0 mL, 1.0 mmole) was added to a suspension of methyl (±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetate (397 mg, 0.85 mmole) in THF (4.3 mL) and H_2O (3.3 mL) at RT. The light yellow mixture was stirred at 40 - 50°C for 1 hr, and the resulting homogeneous solution was then stirred at RT for 17.5 hr. The reaction was concentrated, and the resulting oil was dissolved in H_2O (4 mL). The solution was filtered to remove particulates, and the filtrate was

neutralized with 1.0 N HCl (1.0 mL). The yellowish solid was collected and triturated with good stirring with hot 1:1 CH_3CN/H_2O. The resulting solid was collected, washed with plenty of 1:1 CH_3CN/H_2O, and dried in high vacuum (40°C) to afford the title compound (327.9 mg, 85%) as a colorless powder: HPLC (PRP-1®, 15% CH_3CN/H_2O containing 0.1% TFA) K' = 4.6; MS (ES) m/e 452.2 (M + H)$^+$. Anal. Calcd for $C_{23}H_{25}N_3O_5$: C, 61.19; H, 5.58; N, 15.51. Found: C, 61.18; H, 5.58; N, 15.39.

Example 3

Preparation of (±)-4-[4-[[[(1H-benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-phenylbutanoic acid

a) Ethyl 3-hydroxy-4-(4-methoxyphenyl)-3-phenylbutanoate

Anhydrous EtOAc (4.3 mL, 44 mmole) was added dropwise over 5 - 6 min to a solution of lithium bis(trimethylsilyl)amide (1.0 M in THF, 40 mL, 40 mmole) in dry THF (60 mL) in a flame-dried flask at -78°C under argon. The yellow solution was stirred at -78°C for 0.5 hr, then a solution of 2-(4-methoxyphenyl)-1-phenylethanone (*Chem. Ber.* **1958**, *91*, 755-759; 4.53 g, 20 mmole) in dry THF (20 mL) was added dropwise over 12 min. Additional THF (2 mL) was used in transfer. After 0.5 hr, The reaction was quenched with satd NH_4Cl (120 mL) and warmed to RT. EtOAc extraction, drying ($MgSO_4$), concentration, and silica gel chromatography (20% EtOAc/hexanes) gave the title compound (6.13 g, 96%) as a light yellow oil: TLC R_f (20% EtOAc/hexanes) 0.34; MS (ES) m/e 315.2 (M + H)$^+$.

b) Ethyl 4-(4-methoxyphenyl)-3-phenylbutanoate

Boron trifluoride etherate (4.8 mL, 39 mmole) was added dropwise over 3 min to a solution of ethyl 3-hydroxy-4-(4-methoxyphenyl)-3-phenylbutanoate (6.13 g, 19.5 mmole) and triethylsilane (6.2 mL, 39 mmole) in anhydrous CH_2Cl_2 (49 mL) at 0°C under argon. The reaction was stirred at RT overnight, then was quenched with 5% $NaHCO_3$ (100 mL). The mixture was stirred briskly for 10 min, then was separated. The aqueous layer was extracted with CH_2Cl_2 (100 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was reconcentrated from hexanes (to remove CH_2Cl_2) to leave a yellow oil. This was dissolved in absolute EtOH (100 mL), and 10% Pd/C (775 mg, 1.95 mmole) was added. The mixture was shaken on a Parr apparatus at RT under H_2 (50 psi) for 2 hr, then was filtered through celite®. The filtrate was concentrated, and the residue was

chromatographed on silica gel (15 % EtOAc/hexanes). The title compound (5.27 g, 91%) was obtained as a colorless oil: TLC R_f (15% EtOAc/hexanes) 0.40; MS (ES) m/e 299.2 $(M + H)^+$.

c) Ethyl 4-(4-hydroxyphenyl)-3-phenylbutanoate

Anhydrous aluminum trichloride (4.49 g, 33.7 mmole) was added all at once to solution of ethyl 4-(4-methoxyphenyl)-3-phenylbutanoate (2.01 g, 6.74 mmole) and ethanethiol (2.5 mL, 33.7 mmole) in anhydrous CH_2Cl_2 (67 mL) at 0°C under argon. The yellow solution was warmed to RT and stirred for 3 hr, then was recooled to 0°C and quenched with cold 3 N HCl (67 mL). The mixture was stirred for 5 min, then was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. Silica gel chromatography (25% EtOAc/hexanes) gave the title compound (1.84 g, 96%) as a colorless oil: TLC R_f (30% EtOAc/hexanes) 0.47; MS (ES) m/e 285.2 $(M + H)^+$.

d) Ethyl 3-phenyl-4-[4-(trifluoromethanesulfonyloxy)phenyl]butanoate

Trifluoromethanesulfonic anhydride (1.4 mL, 8.4 mmole) was added rapidly dropwise to a solution of ethyl 4-(4-hydroxyphenyl)-3-phenylbutanoate (1.84 g, 6.47 mmole) and 2,6-lutidine (1.5 mL, 12.9 mmole) in anhydrous CH_2Cl_2 (32 mL) at -78°C under argon. After 0.5 hr, the yellow solution was warmed to RT and stirred for 1 hr. The reaction was diluted with Et_2O (150 mL) and washed sequentially with 1.0 N HCl (15 mL), 5% $NaHCO_3$ (15 mL), and saturated brine(15 mL). Drying ($MgSO_4$), concentration, and silica gel chromatography (15% EtOAc/hexanes) gave the title compound (2.62 g, 97%) as a nearly colorless oil: TLC R_f (20% EtOAc/hexanes) 0.55; MS (ES) m/e 417.0 $(M + H)^+$.

e) Ethyl 4-(4-carboxyphenyl)-3-phenylbutanoate

A mixture of ethyl 3-phenyl-4-[4-(trifluoromethanesulfonyloxy)phenyl]butanoate (2.62 g, 6.29 mmole), anhydrous KOAc (2.47 g, 25.16 mmole), $Pd(OAc)_2$ (70.6 mg, 0.31 mmole), dppf (697.4 mg, 1.26 mmole), and anhydrous DMSO (31 mL) was purged with carbon monoxide (three evacuation/ carbon monoxide purge cycles, followed by bubbling carbon monoxide through the mixture for 5 min), then was heated at 70°C under a balloon of carbon monoxide. After 3.5 hr, the reaction was diluted with H_2O (31 mL), cooled in ice, and acidified with 1.0 N HCl (25 mL). CH_2Cl_2 extraction (2 x 100 mL), drying ($MgSO_4$), concentration, and reconcentration from toluene left a

reddish-orange liquid. Silica gel chromatography (1% AcOH in 7:3 toluene/EtOAc) gave the title compound (1.78 g, 91%) as a cream-colored solid: TLC R_f (1% AcOH in 7:3 toluene/EtOAc) 0.47; MS (ES) m/e 313.2 $(M + H)^+$.

f) Ethyl (±)-4-[4-[[[(1H-benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-phenylbutanoate

EDC (230 mg, 1.2 mmole) was added to a solution of ethyl 4-(4-carboxyphenyl)-3-phenylbutanoate (312.4 mg, 1.0 mmole), 2-(methylaminomethyl)benzimidazole dihydrochloride (281 mg, 1.2 mmole), HOBt · H_2O (162 mg, 1.2 mmole), and diisopropylethylamine (0.70 mL, 4.0 mmole) in anhydrous CH_3CN (5 mL) at RT. After 18 hr, the reaction was concentrated, and the brown residue was chromatographed on silica gel (5% MeOH in 1:1 EtOAc/$CHCl_3$). The title compound (439.2 mg, 96%) was obtained as a light orange foam: TLC R_f (5% MeOH in 1:1 EtOAc/$CHCl_3$) 0.50; MS (ES) m/e 456.2 $(M + H)^+$.

g) (±)-4-[4-[[[(1H-Benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-phenylbutanoic acid

A solution of ethyl (±)-4-[4-[[[(1H-benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-phenylbutanoate (439.2 mg, 0.96 mmole) and 1.0 N NaOH (1.2 mL, 1.2 mmole) in EtOH (8.4 mL) was stirred at 50°C. After 24 hr, the reaction was concentrated to dryness and the residue was purified by ODS chromatography (35% MeOH/H_2O). Concentration and lyophilization gave the title compound (412.2 mg, 86%) as a colorless powder: HPLC (PRP-1®, 35% CH_3CN/H_2O containing 0.1% TFA) K' = 1.4; MS (ES) 428 $(M + H)^+$, 450 $(M + Na)^+$. Anal. Calcd for $C_{26}H_{24}N_3O_3Na \cdot 2.75\ H_2O$: C, 62.58; H, 5.96; N, 8.42. Found: C, 62.34; H, 5.84; N, 8.44.

Example 4

Preparation of (±)-4-[4-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-(dimethylaminocarbonyl)butanoic acid

a) tert-Butyl 4-bromobenzoate

Trifluoromethanesulfonic acid (0.18 mL, 2 mmole) was added dropwise to a mixture of 4-bromobenzoic acid (20.10 g, 100 mmole), anhydrous CH_2Cl_2 (100 mL), and condensed isobutylene (-78°C; 100 mL), and the resulting mixture was allowed to reflux under a dry ice/acetone condenser. After 40 min, more isobutylene (30

mL) was added, and reflux was continued for an additional 20 min. The reaction was poured into Et_2O (500 mL) and washed sequentially with 1.0 N KOH (2 x 50 mL), H_2O (50 mL), and satd brine (50 mL). Drying ($MgSO_4$), concentration, and silica gel chromatography (5% EtOAc/hexanes) gave the title compound (15.28 g, 59%) as a light yellow oil: TLC R_f (5% EtOAc/hexanes) 0.59; MS (ES) m/e 259/257 $(M + H)^+$.

b) Methyl 3-[4-(tert-butoxycarbonyl)phenyl]propenoate

A solution of tert-butyl 4-bromobenzoate (5.14 g, 20 mmole), methyl acrylate (9.1 mL, 100 mmole), $Pd(OAc)_2$ (224.5 mg, 1 mmole), tri-*o*-tolylphosphine (608.8 mg, 2 mmole), and diisopropylethylamine (7.0 mL, 40 mmole) in propionitrile (100 mL) was heated at reflux for 3 hr, then was concentrated on the rotavap. The residue was diluted with Et_2O (200 mL) and washed sequentially with 1.0 N HCl (2 x 50 mL), 5% $NaHCO_3$ (50 mL), and satd brine (50 mL). Drying ($MgSO_4$), concentration, and silica gel chromatography (15% EtOAc/hexanes) gave the title compound (3.34 g, 64%) as a light yellow solid: TLC R_f (20% EtOAc/hexanes) 0.51; MS (ES) m/e 263.0 $(M + H)^+$.

c) Methyl 3-[4-(tert-butoxycarbonyl)phenyl]propanoate

10% Pd/C (2.71 g, 2.55 mmole) was added to a solution of methyl 3-[4-(tert-butoxycarbonyl)phenyl]propenoate (3.34 g, 12.73 mmole) in EtOAc (65 mL) and MeOH (65 mL), and the mixture was shaken on a Parr apparatus at RT under H_2 (50 psi). After 3 hr, the reaction was filtered through celite®, and the filtrate was concentrated to dryness on the rotavap. Reconcentration from hexanes left the title compound (3.27 g, 97%) as a cloudy, grayish oil: TLC R_f (20% EtOAc/hexanes) 0.63; MS (ES) m/e 265.0 $(M + H)^+$.

d) 3-[4-(tert-Butoxycarbonyl)phenyl]propanoic acid

A mixture of methyl 3-[4-(tert-butoxycarbonyl)phenyl]propanoate (3.27 g, 12.37 mmole), 1.0 N LiOH (14.8 mL, 14.8 mmole), THF (31 mL), and H_2O (16 mL) was stirred at RT for 1.5 hr, then was concentrated on the rotavap to remove the THF. The aqueous solution was washed with Et_2O (2 x 30 mL), and the Et_2O layers were discarded. The aqueous layer was acidified with 1.0 N HCl (ca. 17 mL), and the mixture was extracted with $CHCl_3$ (3 x 50 mL). Drying (Na_2SO_4) and concentration gave the title compound (3.04 g, 98%) as a colorless powder: mp 88.5 - 89.5°C; MS (DCI/NH_3) m/e 268.0 $(M + NH_4)^+$.

e) N,N-Dimethyl 3-[4-(tert-butoxycarbonyl)phenyl]propanamide

EDC (2.09 g, 10.88 mmole) was added to a solution of 3-[4-(tert-butoxycarbonyl)phenyl]propanoic acid (2.27 g, 9.07 mmole), dimethylamine hydrochloride (0.88 g, 10.88 mmole), HOBt · H_2O (1.47 g, 10.88 mmole), and diisopropylethylamine (3.2 mL, 18.14 mmole) in anhydrous CH_3CN (45 mL) at RT. After 19.5 hr, the reaction was concentrated, and the residue was chromatographed on silica gel (EtOAc). The title compound (2.46 g, 98%) was obtained as a colorless oil: TLC R_f (EtOAc) 0.52; MS (ES) m/e 278.4 $(M + H)^+$.

f) Ethyl 4-[4-(tert-butoxycarbonyl)phenyl]-3-(dimethylaminocarbonyl)butanoate

A solution of lithium bis(trimethylsilyl)amide in THF (1.0 M, 5.8 mL, 5.8 mmole) was added dropwise over 2.5 min to a solution of N,N-dimethyl 3-[4-(tert-butoxycarbonyl)phenyl]propanamide (1.34 g, 4.83 mmole) in dry THF (48 mL) at -78°C under argon. The yellow solution was stirred at -78°C for 0.5 hr, then ethyl bromoacetate (2.7 mL, 24.15 mmole) was added over 15 sec down the walls of the flask (to precool). After 0.5 hr, the reaction was poured into satd NH_4Cl (50 mL), and the mixture was extracted with EtOAc (2 x 100 mL). Drying ($MgSO_4$), concentration, and reconcentration from xylenes left a light yellow oil. Silica gel chromatography (1:1 EtOAc/hexanes) gave the title compound (453.5 mg, 26%) as a light yellow oil: TLC R_f (1:1 EtOAc/hexanes) 0.44; MS (ES) m/e 364.2 $(M + H)^+$.

g) Ethyl 4-(4-carboxyphenyl)-3-(dimethylaminocarbonyl)butanoate

TFA (2.3 mL) was added all at once to a solution ethyl 4-[4-(tert-butoxycarbonyl)phenyl]-3-(dimethylaminocarbonyl)butanoate (168.6 mg, 0.46 mmole) in anhydrous CH_2Cl_2 (2.3 mL) at 0C. The solution was stirred at RT for 0.5 hr, then was concentrated to dryness on the rotavap. The residue was reconcentrated from toluene to afford the title compound as a light yellow oil: MS (ES) m/e 308.0 $(M + H)^+$.

h) Ethyl (±)-4-[4-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-(dimethylaminocarbonyl)butanoate

EDC (105.8 mg, 0.55 mmole) was added to a solution of ethyl 4-(4-carboxyphenyl)-3-(dimethylaminocarbonyl)butanoate (0.46 mmole), 2-(methylaminomethyl)benzimidazole dihydrochloride (129.2 mg, 0.55 mmole), HOBt · H_2O (74.6 mg, 0.55 mmole), and diisopropylethylamine (0.32 mL, 1.84 mmole) in anhydrous CH_3CN (2.3 mL) at RT. After 22 hr, the reaction was concentrated, and the yellow residue was chromatographed on silica gel (10%

MeOH in 1:1 EtOAc/$CHCl_3$). The title compound (191.5 mg, 92%) was obtained as a light yellow oil: TLC R_f (10% MeOH in 1:1 EtOAc/$CHCl_3$) 0.44; MS (ES) m/e 451 $(M + H)^+$.

i) (±)-4-[4-[[[(Benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-(dimethylaminocarbonyl)butanoic acid

A solution of ethyl (±)-4-[4-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-(dimethylaminocarbonyl)butanoate (191.5 mg, 0.43 mmole) and 1.0 N LiOH (0.52 mL, 0.52 mmole) in THF (2.2 mL) and H_2O (1.6 mL) was stirred at RT for 17 hr, then was acidified with TFA (0.10 mL, 1.29 mmole). Concentration left an aqueous residue which was purified by ODS chromatography (17% CH_3CN/H_2O containing 0.1% TFA; chromatographed again using 15% CH_3CN/H_2O containing 0.1% TFA). Concentration and lyophilization gave the title compound (133.4 mg, 47%) as a colorless powder: HPLC (PRP-1®, 20% CH_3CN/H_2O containing 0.1% TFA) K' = 1.3; MS (ES) m/e 423.2 $(M + H)^+$. Anal. Calcd for $C_{23}H_{26}N_4O_4 \cdot 2\ CF_3CO_2H \cdot 0.5\ H_2O$: C, 49.17; H, 4.43; N, 8.49. Found: C, 49.13; H, 4.62; N, 8.52.

Example 5

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid, [(2,2-dimethyl-2-methoxyacetyl)oxy]methyl ester

a) (S)-2,3,4,5-Tetrahydro-7-[[[[1-(tert-butoxycarbonyl)benzimidazol-2-yl]methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

To a mixture of (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid (444 mg, 1.0 mmol), triethylamine (0.1464 mL, 1.05 mmol) in DMF (8 mL), was added dropwise di-tert-butyl dicarbonate (230 mg, 1.05 mmol) in DMF (2 mL). The reaction mixture was stirred at RT for 18 h. An aliquot was assayed to indicate only 50% conversion. Another quantity of triethylamine and di-tert-butyl dicarbonate were added and stirring was continued for another 18 h. An aliquot still indicated some unreacted material, so a third quantity of reagents was added and the reaction was stirred for another 18 h. The reaction mixture was concentrated to dryness and the residual oil was triturated with water, filtered and vacuum dried at

40-50°C, to give a white solid of the title compound (0.442 g, 85%). MS (ES) m/e 522.4 $[M+H]^+$.

b) (S)-2,3,4,5-Tetrahydro-7-[[[[1-(tert-butoxycarbonyl)benzimidazol-2-yl]methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid, [(2,2-dimethyl-2-methoxyacetyl)oxy]methyl ester

To a solution of the compound of Example 5a, (0.209 g, 0.4 mmol) in dry acetone (10 mL) was added anhydrous potassium carbonate (0.25 g, 1.8 mmol). The reaction mixture was stirred at RT and under argon for 1 h. 2-methoxy-2-methylpropanoic acid chloromethyl ester, US Patent 4,602,012, July 22, 1986, (0.334 g, 2.0 mmol) was then added, followed by tetrabutylammonium iodide (0.03 g, 0.08 mmol). The reaction was stirred at RT under argon for 48 h. It was then filtered and the filtrate was concentrated to a yellow oily residue of the title compound (0.67g , quantitative yield). TLC R_f 0.48 (silica gel, 6% methanol in methylene chloride). MS (ES) m/e 652.2 $[M+H]^+$.

c) (S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid, [(2,2-dimethyl-2-methoxyacetyl)oxy]methyl ester

To a solution of the compound in Example 5b (0.67 g, 1 mmol) in methylene chloride (5 mL) was added TFA (1 mL). The reaction was stirred at RT under argon for 4 h. It was concentrated to dryness, and the residue was evaporated with methylene chloride three times to remove TFA traces, to give the title compound (0.4 g, 73%). This was purified on a flash silica column (step gradient, 2-3% methanol in methylene chloride). The fractions containing the pure compound were collected, concentrated to yield the title compound (65 mg) as an off-white solid. MS (ES) m/e 552.2 $[M+H]^+$. ^1H NMR (400 MHz, ($CDCl_3$) δ 7.6 (br s, 1H), 7.22 (m, 6H), 6.5 (d, 1H), 5.85 (d, 1H), 5.8 (d, 1H), 5.4 (d, 1H), 5.05 (m, 1H), 4.79 (q, 2H), 4.3 (d, 1H), 3.7 (d, 1H), 3.25 (s, 3H), 3.15 (s, 3H), 3.05 (s, 3H), 3.02 (dd, 1H), 2.7 (dd, 1H), 1.4 (s, 6H). Anal. Calcd for $C_{28}H_{33}N_5O_7 \cdot 1.25\ H_2O$: C, 58.58; H, 6.23; N, 12.20. Found: C, 58.60, H, 5.94, N, 12.00.

Example 6

Preparation of (±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-(N-hydroxy)acetamide

a) (±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazole-2-yl)methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-(N-hydroxy)acetamide

NaOMe (Aldrich, 25 wt. % solution in MeOH, 2.2 mL, 9.7 mmole) was added to a solution of hydroxylamine hydrochloride (0.67 g, 9.7 mmole) in MeOH (40 mL) at 45°C, and the mixture was stirred for 5 min. Methyl (±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.82 g, 1.9 mmole) was suspended in MeOH (2 mL) and THF (15 mL) and added dropwise to the above solution. The reaction was then stirred at 45°C for 24 h. The mixture was concentrated in vacuo, and was then treated with 10% CH_3CN/H_2O containing 0.1% TFA (5 mL). All material dissolved, and then a solid precipitated out. Half of this material was dissolved in the mobile phase by addition of excess TFA and was purified by. preparative HPLC (YMC ODS-AQ, 50 x 250 mm, flow rate = 80 mL/min, 10% CH_3CN/H_2O containing 0.1% TFA; t_R = 57 min) to yield the title compound (91 mg, 22%) as a white solid. MS (ES) m/e 423.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.06 (bt, J = 4 Hz, 1H), 7.77 (m, 2H), 7.58 (m, 2H), 7.50 (m, 2H), 6.60 (d, J = 10 Hz, 1H), 6.40 (bs, 1H), 5.52 (d, J = 19 Hz, 1H), 5.18 (bt, J = 9 Hz, 1H), 4.85 (d, J = 6 Hz, 1H), 3.83 (d, J = 19 Hz, 1H), 2.95 (s, 3H), 2.60 (dd, J = 17, 9 Hz, 1H), 2.28 (dd, J = 15, 7 Hz, 1H). Anal. Calcd for $C_{21}H_{22}N_6O_4 \cdot 1.5\ C_2HF_3O_2 \cdot 1.0\ H_2O$): C, 47.14; H, 4.20; N, 13.74. Found: C, 46.95; H, 4.24; N, 13.37.

Example 7

Preparation of (±)-2,3,4,5-tetrahydro-7-[3-(benzimidazol-2-yl)phenyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) 2-(3-Iodophenyl)benzimidazole

To a cold solution of 3-iodobenzoic acid (5.0 g, 20 mmol) and Et_3N (3.7 mL, 26 mmol) in THF (50 mL) was added isobutylchloroformate (2.9 mL, 21 mmol). The solution was stirred for 1 h at 10°C. All of the solution was added slowly to a solution of 1,2-diaminobenzene (2.2 g, 20 mmol) in THF (50 mL). After 18 hr, the reaction was concentrated and the residue was partitioned between EtOAc and 5% Na_2CO_3. The layers were separated and the EtOAc layer was washed with water. Concentration of the organic layer gave a residue which was treated with EtOAc and allowed to stand for 15 min. Filtration gave a solid which was treated with AcOH (50 mL) and heated to 110°C. After 18 hr, the solution was concentrated. The

residue was treated with EtOAc and the solution was filtered to give the title compound (3.14 g, 50%): MS (ES) m/e 321.2 $(M+H)^+$.

b) 2-[(3-Tributylstannyl)phenyl]benzimidazole

A solution of 2-(3-iodophenyl)benzimidazole (1.0 g, 3.1 mmol), bistributyltin (3.9 mL, 6.2 mmol) and $PdCl_2(PPh_3)_2$ (100 mg, 0.14 mmol) in DMF (10 mL) was heated to 90°C under argon. After 2 hr, the solution was concentrated. The residue was treated with hexane and filtered. EtOAc was added and the solution was filtered. The filtrate was concentrated to give the title compound (812 mg, 54%): MS (ES) m/e 485.4 $(M+H)^+$.

c) Methyl (±)-2,3,4,5-tetrahydro-1-(tert-butoxycarbonyl)-7-iodo-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

To a solution of methyl-7-iodo-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (1.6 g, 4.3 mmol) and DMAP (10 mg, 0.08 mmol) in CH_3CN (10 mL) was added di-tert-butyl dicarbonate (2.0 g, 8.6 mmol), and the solution was stirred at RT. Additional di-tert-butyl dicarbonate (a total of 8 g , 34.4 mmol) was added periodically until the reaction went to completion. Concentration and silica gel chromatography gave the title compound (1.8 g, 90%): MS (ES) m/e 497.2 $(M+Na)^+$.

d) Methyl (±)-2,3,4,5-tetrahydro-7-[3-(benzimidazol-2-yl)phenyl]-1-(tert-butoxycarbonyl)-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

A mixture of 2-[(3-tributylstannyl)phenyl]benzimidazole (0.24 g, 0.5 mmol), methyl (±)-1-(tert-butoxycarbonyl)-7-iodo-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.223 g, 0.7 mmol), CuI (10 mg, 0.05 mmol), and $PdCl_2(PPh_3)_2$ (40 mg, 0.05 mmol) in DMF (10 mL) was heated to 100°C under argon. After 18 hr, the solution was concentrated. Silica gel chromatography gave the title compound (0.06 g, 22%): MS (ES) m/e 541.5 $(M+H)^+$.

e) Methyl (±)-2,3,4,5-tetrahydro-7-[3-(benzimidazol-2-yl)phenyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

A solution of methyl (±)-2,3,4,5-tetrahydro-7-[3-(benzimidazol-2-yl)phenyl]-1-(tert-butoxycarbonyl)-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.06 g, 0.11 mmol) in 4 M HCl/dioxane (3 mL) was stirred for 1 hr at RT. The solution was concentrated to give the title compound (0.05 g, 100%): MS (ES) m/e 441.4 $(M+H)^+$.

f) (±)-2,3,4,5-Tetrahydro-7-[3-(benzimidazol-2-yl)phenyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

1.0 N NaOH (0.22 mL, 0.22 mmol) was added dropwise to a solution of methyl (±)-2,3,4,5-tetrahydro-7-[3-(benzimidazol-2-yl)phenyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.05 g, 0.11 mmol) in 1:1 MeOH/H_2O (2 mL) at RT, and the resulting solution was stirred for 18 hr, then was concentrated. The residue was dissolved in H_2O and the solution was acidified with AcOH to pH 4 (Litmus paper). Filtration gave the title compound (0.005 g, 10%): ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.4-2.9 (m, 2H), 3.0-3.1 (s, 3H), 3.8-4.0 (d, 1H), 5.0-5.1 (m, 1H), 5.5-5.6 (d, 1H), 6.7-6.8 (d, 1H), 7.5-8.5 (m, 11H); MS (ES) m/e 427.5 $(M+H)^+$. Anal. Calcd for $C_{25}H_{22}N_4O_3 \cdot 1.5\ HCl \cdot 1.0\ AcOH \cdot 0.5\ H_2O$: C, 58.94; H, 5.22; N, 10.18. Found: C, 59.00; H, 5.15; N, 9.92.

Example 8

Preparation of (±)-2,3,4,5-tetrahydro-4-methyl-3-oxo-7-[[[(phenanthrimidazol-2-yl)methyl]amino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid

a) 2-[[(N-Benzyloxycarbonyl)amino]methyl]phenanthrimidazole

Following the general procedure of Example 7(a), except substituting N-Cbz-glycine for the 3-iodobenzoic acid, and 9,10-diaminophenanthrene for the 1,2-diaminobenzene, the title compound (0.41 g, 45%) was prepared: MS (ES) m/e 382.4 $(M+H)^+$.

b) 2-(Aminomethyl)phenanthrimidazole

A solution of 2-[[(N-benzyloxycarbonyl)amino]methyl]phenanthrimidazole (0.2 g, 0.52 mmol) in 30% HBr in acetic acid (0.8 mL) was stirred at RT for 1 hr. The solution was concentrated and the residue was treated with Et_2O. Filtration gave the title compound (0.138 g, 80%) as an oily residue: MS (ES) m/e 248.3 $(M+H)^+$.

c) Methyl (±)-2,3,4,5-tetrahydro-4-methyl-3-oxo-7-[[[(phenanthrimidazol-2-yl)methyl]amino]carbonyl]-1H-1,4-benzodiazepine-2-acetate

EDC (0.08 g, 0.42 mmol) was added to a solution of 2-(aminomethyl)phenanthrimidazole (0.138 g, 0.42 mmol), methyl (±)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (0.123 g, 0.42 mmol), HOBt · H_2O (0.063 g, 0.42 mmol) and Et_3N (0.14 mL, 1 mmol) in anhydrous

DMF (5 mL) at RT. After 18 hr, the reaction was concentrated, and the residue was partitioned between EtOAc and 5% $NaHCO_3$. The layers were separated and the organic layer was washed with H_2O. Drying (Na_2SO_4) and concentration gave the title compound (0.2 g, 90%): MS (ES) m/e 522.4 $(M+H)^+$.

d) (±)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[(phenanthrimidazol-2-yl)methyl]amino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure of Example 7(f), methyl (±)-2,3,4,5-tetrahydro-4-methyl-3-oxo-7-[[[(phenanthrimidazol-2-yl)methyl]amino]carbonyl]-1H-1,4-benzodiazepine-2-acetate (0.2 g, 0.38 mmol) was saponified and purified to give the title compound (0.014 g, 10%): MS (ES) m/e 508.5 $(M+H)^+$. Anal. Calcd for $C_{29}H_{25}N_5O_4 \cdot 1.0$ TFA $\cdot 3.0 H_2O$: C, 55.11; H, 4.77; N, 10.37. Found: C, 55.38; H, 5.13; N, 10.74.

Example 9

Preparation of methyl (±)-7-carboxy-4-(2,2,2-trifluoroethyl)-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate

a) tert-Butyl 3-[(2,2,2-trifluoroethyl)amino]methyl-4-nitrobenzoate

tert-Butyl 3-bromomethyl-4-nitrobenzoate (2.4 g, 8 mmol)was dissolved in dry THF (50 mL), and 2,2,2-trifluoroethylamine (3 mL, 38 mmol) was added all at once. The orangish-yellow solution was stirred at RT for 40 min, then was concentrated to remove the THF. The residue was diluted with Et_2O (100 mL) and washed twice with 10 % aqueous Na_2CO_3 (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$). Concentration and silica gel chromatography (2.5% - 10% EtOAc/hexanes) gave the title compound (1.6 g, 63%) as a yellow oil: ^1H NMR (250 MHz, $CDCl_3$) δ 8.21 (d, J = 1.3 Hz, 1H), 8.03 (dd, J = 8.4, 1.3 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 4.20 (s, 2H), 3.24(q, J = 9.3 Hz, 2H), 1.62 (s, 9H).

b) tert-Butyl 3-[[N-(2,2,2-trifluoroethyl)-N-(tert-butoxycarbonyl)]amino]methyl-4-nitrobenzoate

Di-tert-butyl dicarbonate (2.15 g, 10 mmol) was added all at once to a solution of tert-butyl 3-[(2,2,2-trifluoroethyl)amino]methyl-4-nitrobenzoate (1.6 g, 5 mmol) in CH_2Cl_2 (25 mL) at RT. The reaction was concentrated and heated to 50°C under vacuum for 18 hours. Silica gel chromatography (2% - 5% EtOAc/hexanes) gave the title compound (2 g, 96%) as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ

7.85-8.15 (m, 3H), 4.75-5.05 (m, 2H), 3.80-4.10 (m, 2H), 1.60 (s, 9H), 1.15-1.80 (m, 9H).

c) tert-Butyl 4-amino-3-[[N-(2,2,2-trifluoroethyl)-N-(tert-butoxycarbonyl)]amino]methylbenzoate

10% Pd/C (.4 g, .4 mmol) was added to a solution of tert-butyl 3-[[N-(2,2,2-trifluoroethyl)-N-(tert-butoxycarbonyl)]amino]methyl-4-nitrobenzoate (2.0 g, 5 mmol) in EtOAc (20 mL), and the mixture was shaken on a Parr apparatus at RT under H_2 (55 psi). After 4 h, the reaction was filtered through celite®, and the filtrate was concentrated to afford the title compound (1.9 g, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, J = 8.5 Hz, 1.8 Hz, 1H), 7.68 (d, J = 1.8 Hz, 1H), 6.62 (d, J = 8.4 Hz, 1H), 4.53 (s, 2H), 3.69 (m, 2H), 1.58 (s, 9H), 1.51(m, 9H).

d) tert-Butyl (±)-4-[2-(1,4-dimethoxy-1,4-dioxobutyl)amino]-3-[[N-(2,2,2-trifluoroethyl)-N-(tert-butoxycarbonyl)]amino]methylbenzoate

A solution of tert-butyl 4-amino-3-[[N-(2,2,2-trifluoroethyl)-N-(tert-butoxycarbonyl)]amino]methylbenzoate (1.9 g, 5 mmol) and dimethylacetylene dicarboxylate (0.58 mL, 5.5 mmol) in MeOH (10 mL) was heated at reflux for 60 min, then was cooled to RT. The resulting solution was combined with MeOH (20 mL) and 10% Pd/C (0.5 g, .5 mmol), and the mixture was shaken on a Parr apparatus at RT under H_2 (50 psi). After 3 h, the reaction was filtered through celite®, and the filtrate was concentrated on the rotavap. The title compound (1.6 g, 62%) was obtained as a faintly yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, J = 8.4, 2.0 Hz, 1H), 7.68 (d, J = 2.0 Hz, 1H), 6.65 (d, J = 8.4 Hz, 1H), 6.15 (br s, 1H), 4.55-4.70 (m, 2H), 4.40 (1/2 AB, J = 15.3 Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.35-3.50 (m, 2H), 2.95 (dd, J = 16.9, 6.8 Hz, 1H), 2.84 (dd, J = 16.9, 6.9 Hz, 1H), 1.56 (s, 18H).

e) Methyl (±)-7-carboxy-4-(2,2,2-trifluoroethyl)-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate

TFA (7 mL) was added all at once to a solution of tert-butyl (±)-4-[2-(1,4-dimethoxy-1,4-dioxobutyl)amino]-3-[[N-(2,2,2-trifluoroethyl)-N-(tert-butoxycarbonyl)]amino]methylbenzoate (1.6 g, 3 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0°C, and the faintly yellow solution was warmed to RT. After 2 h, the solution was concentrated on the rotavap, and the residue was reconcentrated from toluene (to remove residual TFA). The resulting oil was combined with toluene (10 mL) and Et_3N (2 mL, 15 mmol), and the mixture was heated to reflux under argon. After 18 hr the solution was allowed to cool and was concentrated to dryness under

vacuum. The residue was dissolved in a minimum of MeOH (ca. 15 mL) at reflux, diluted with H_2O (10 mL), and acidified with glacial AcOH (4 drops). The mixture was kept in the refrigerator overnight then was filtered. The solid was dried under high vacuum to afford the title compound (0.80 g, 76%) as a tan powder: ^1H NMR (400 MHz, DMSO-d_6) δ 7.61 (2, 1H), 7.57 (dd, J = 8.5, 2 Hz, 1H), 6.63 (d, J = 2 Hz, 1H), 6.59 (d, J = 8.5 Hz, 1H), 5.59 (d, J = 16.7 Hz, 1H), 5.25 (m, 1H), 4.28 (m, 2H), 4.15 (d, J = 16.7 Hz, 1H), 3.61 (s, 3H), 2.86 (dd, J = 16.8, 8.7 Hz, 1H), 2.74 (dd, J = 16.8, 5.4 Hz, 1H).

f) Methyl (±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetate

EDC (0.16 g, 0.86 mmol) was added at RT to a solution of methyl (±)-7-carboxy-4-(2,2,2-trifluoroethyl)-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (0.20 g, 0.71 mmol), HOBt · H_2O (0.12 g, 0.86 mmol), 2-aminomethylbenzimidazole dihydrochloride (0.19 g, 0.86 mmol), DIEA (0.5 mL, 2.8 mmol), and acetonitrile (5 mL) under argon. The resulting solution was stirred at RT overnight, then was concentrated. The residue was partitioned between ethyl acetate and water, and the layers were separated. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated. Silica gel chromatography (1% - 10% CH_3OH in CH_2Cl_2) gave the title compound (0.12 g, 44%) as a tan solid: NMR (400 MHz, DMSO-d_6) δ 8.59 (t, J = 5 Hz, 1H), 7.61 (m, 2H), 7.50 (m, 2H), 7.16 (m, 2H), 6.57 (d, J = 11.1 Hz, 1H), 6.17 (d, J = 5 Hz, 1H), 5.53 (d, J = 16.7 Hz, 1H), 5.13 (m, 1H), 4.75 (m, 2H), 4.10 (m, 2H), 3.62 (s, 3H), 2.94 (dd, J = 16.8, 8.5 Hz, 1H), 2.69 (dd, J = 16.8, 5.4 Hz, 1H).

g) (±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid

A solution f methyl(±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetate (0.12 g, 0.25 mmol) and lithium hydroxide monohydrate (0.017 g, 0.4 mmol) in THF (10 mL), CH_3OH (2 mL), and H_2O (2 mL) was stirred at RT overnight. It was then concentrated and the residue was dissolved in water. The solution was brought to pH 4 with 3 N HCl, then was refrigerated for 1 hour. The resulting solid was collected by filtration and dried to give the title compound (0.11 g, 90%) as a white solid: Ms (ES) m/e 476 $[M+H]^+$. Anal. Calcd for $C_{22}H_{20}N_5F_3O_4 \cdot 1.25\ H_2O$: C, 53.07; H, 4.55; N, 14.06. Found: C, 52.85; H, 4.36; N, 13.98.

Example 10

Preparation of (±)-2,3,4,5-tetrahydro-7-[[[benzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (±)-2,3,4,5-tetrahydro-7-[[[benzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetate

Using the procedures of Example 9(f), except substituting 2-(methylaminomethyl)benzimidazole dihydrochloride for the 2-aminomethylbenzimidazole dihydrochloride, the title compound was prepared: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 2 H), 7.37 (m, 2 H), 7.25 (m, 2 H), 6.54 (d, J = 8 Hz, 1 H), 5.46 (d, J = 16.7 Hz, 1 H), 5.20 (m, 1 H), 5.04 (s, 2 H), 4.71 (m, 1 H), 4.17 (m, 1 H), 3.94 (m, 1 H), 3.92 (d, J = 16.7, 1 H), 3.74 (s, 3 H), 3.23 (s, 3 H), 2.98 (m, 1 H), 2.74 (m, 1 H).

b) (±)-2,3,4,5-Tetrahydro-7-[[[benzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid

Using the procedure of Example 9(g), methyl (±)-2,3,4,5-tetrahydro-7-[[[benzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetate was saponified to afford the title compound: MS (ES) m/e 490.2 [M+H]+. Anal. Calcd for $C_{23}H_{22}N_5F_3O_4 \cdot 2.25\ H_2O$: C, 52.12; H, 5.04; N,13.21. Found: C, 52.00; H, 5.12; N, 13.09.

Example 11

Preparation of (±)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (±)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetate

Using the procedures of Example 9(f), except substituting 2-(aminomethyl)-4-aza-5-methylbenzimidazole dihydrochloride for the 2-aminomethylbenzimidazole dihydrochloride, the title compound was prepared: MS (ES) m/e 505.2 $(M + H)^+$.

b) (±)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid

Using the procedure of Example 9(g), methyl (±)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetate was saponified to afford the title compound: MS (ES) m/e 491.2 $(M+H)^+$. Anal. Calcd for $C_{22}H_{21}N_6F_3O_4 \cdot 2\ 7/8\ H_2O$: C, 48.73; H,4.97; N, 15.50. Found: C, 48.50; H, 4.59; N, 15.33.

Example 12

Preparation of (±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-[2-(3,4-methylenedioxyphenyl)ethyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-[2-(3,4-methylenedioxyphenyl)ethyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate

EDC (0.10 g, 0.55 mmol) was added at RT to a solution of methyl 7-carboxy-4-[2-(3,4-methylenedioxyphenyl)ethyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.14 g, 0.3 mmol), 2-(methylaminomethyl)benzimidazole dihydrochloride (0.12 g, 0.51 mmole), HOBt · H_2O (0.072 g, 0.55 mmol), and DIEA (0.32 mL, 1.84 mmole), in DMF (5 mL) under argon. The resulting solution was stirred at RT overnight, then was concentrated. The residue was partitioned between ethyl acetate and water, and the layers were separated. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. Silica gel chromatography gave the title compound (0.11 g, 59%) as a colorless foam: ^{1}H NMR ($CDCl_3$) δ 7.62 (m, 2H), 7.31 (m, 2H), 7.20 (d, J = 8.1 Hz, 1H), 7.07 (s, 1H), 6.65 (d, J = 7.9 Hz, 1H), 6.60 (s, 1H), 6.55 (d, J = 7.9 Hz, 1H), 6.46 (d, J = 8.1 Hz, 1H), 5.90 (d, J = 5.4 Hz, 2H), 5.26 (d, J = 16.5 Hz, 1H), 5.02 (m, 1H), 4.93, (d, J = 14.6, 1H), 4.83 (d, J = 14.6 Hz, 1H), 4.51 (d, J = 5 Hz, 1H), 3.74 (s, 3H), 3.71 (m, 1H), 3.60 (m, 1H), 3.58 (d, J = 16.5 Hz, 1H), 3.18 (s, 3H), 2.99 (dd, J = 16, 6.8 Hz, 1H), 2.70 (m, 1H).

b) (±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-[2-(3,4-methylenedioxyphenyl)ethyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

To a solution stirred at RT of methyl (±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-[2-(3,4-methylenedioxyphenyl)ethyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.11 g, 0.19 mmol) in THF (1 mL) was added a solution of lithium hydroxide monohydrate (0.01 g, 0.23 mmol) in H_2O (1 mL). The resulting solution was stirred at RT overnight, then was concentrated to dryness. The residue was dissolved in H_2O and the solution was washed with ethyl acetate, then was brought to pH 4 with 3 N HCl. The resulting precipitate was collected by filtration and dried to give the title compound (0.055 g, 51%) as a white solid. MS (ES) m/e 556.2 $[M+H]^+$. Anal. Calcd for $C_{30}H_{29}N_5O_6 \cdot H_2O$: C, 62.82; H, 5.45; N, 12.21. Found: C, 62.69; H, 5.26; N, 12.15.

Example 13

Preparation of (±)-2,3,4,5-tetrahydro-7-[[2-(benzimidazol-2-yl)acetyl]amino]-5-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (±)-2,3,4,5-tetrahydro-7-[[2-(benzimidazol-2-yl)acetyl]amino]-5-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate

EDC (0.27 g, 1.4 mmole) was added at RT to a solution of (±)-2,3,4,5-tetrahydro-7-amino-5-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate (0.40 g, 1.1 mmol), benzimidazole-2-acetic acid (*Archiv. Der Pharmazie* **1960**, *293*, 758; 0.25 g, 1.4 mmol), HOBt · H_2O (0.20 g, 1.5 mmol), and DIEA (0.35 mL, 2 mmol) in acetonitrile (10 mL). The resulting solution was stirred for 2 days, then was concentrated to dryness. The residue was partitioned between ethyl acetate and water, and the layers were separated. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated. Silica gel chromatography (1% - 10% CH_3OH in CH_2Cl_2) gave the title compound (0.21 g, 36%) as an amber foam: MS (ES) m/e 512.2 $[M+H]^+$.

b) (±)-2,3,4,5-Tetrahydro-7-[[2-(benzimidazol-2-yl)acetyl]amino]-5-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid

A solution of methyl (±)-2,3,4,5-tetrahydro-7-[[2-(benzimidazol-2-yl)acetyl]amino]-5-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate (0.21 g, 0.41 mmole) and lithium hydroxide monohydrate (0.022 g, 0.52 mmol) in THF (10 mL) and H_2O (2 mL) was stirred at RT overnight, then was then concentrated. The residue was dissolved in water and the solution was washed with ethyl acetate, then

was brought to pH 4 with 3 N HCl. The resulting precipitate was collected by filtration and dried to give the title compound (0.12 g, 59%) as an off-white solid: MS (ES) m/e 498.2 $[M+H]^+$. Anal. Calcd for $C_{28}H_{27}N_5O_4 \cdot 1.5\ H_2O$: C, 64.11; H, 5.76; N, 13.35. Found: C, 64.36; H, 5.57; N, 13.21.

Example 14

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetamide

a) (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetamide

Methyl (±)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (330 mg, 0.76 mmole) in dry MeOH (10 mL) was cooled in an ice bath as ammonia was bubbled into the solution for 0.5 hr. The reaction was then allowed to sit stoppered at RT for 18 hr. After concentration, the residue was purified by silica gel flash chromatography (90:10 CH_2Cl_2/MeOH) to give the title compound (52%) as a white solid: MS (ES) m/e 421.2 $[M+H]^+$. Anal. Calcd for $C_{22}H_{24}N_6O_3 \cdot 1.5\ H_2O$: C, 59.05; H, 6.08; N, 18.78. Found: C, 58.90; H, 6.04; N, 18.45.

Example 15

Preparation of (±)-5-[[2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepin-2-yl]methyl]tetrazole

a) Methyl (±)-2,3,4,5-tetrahydro-7-(tert-butoxycarbonyl)-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate

Methyl (±)-2,3,4,5-tetrahydro-7-carboxy-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate (1.0 g, 2.6 mmole) was suspended in toluene (10 mL), and N,N-dimethylformamide-di-tert-butyl acetal (5 mL, 20.8 mmole) was added dropwise. The reaction mixture was heated at 80°C for 1.5 hr, then was cooled to RT and poured into 5% Na_2CO_3 solution. The layers were separated, and the aqueous was extracted with toluene (2 x). The combined organic layers were

washed with brine, dried over $MgSO_4$, filtered and evaporated to give the title compound (0.91g, 82%). MS (ES) m/e 439.2 $[M+H]^+$.

b) (±)-2,3,4,5-Tetrahydro-7-(tert-butoxycarbonyl)-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid

A solution of methyl (±)-2,3,4,5-tetrahydro-7-(tert-butoxycarbonyl)-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate (1.5 g, 3.4 mmole) in ethylene glycol dimethyl ether (160 mL) was treated with H_2O (20 mL) and 0.91 N NaOH (5 mL). The reaction was stirred under argon at RT for 24 hr, then was acidified to pH 3 with glacial AcOH, concentrated to a small volume (10 mL), and poured into ice H_2O. The precipitated solid was collected and dried giving the title compound in quantitative yield. MS (ES) m/e 425.2 $[M+H]^+$.

c) (±)-2,3,4,5-Tetrahydro-7-(tert-butoxycarbonyl)-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-[N-(2-cyanoethyl)acetamide]

A solution of (±)-2,3,4,5-tetrahydro-7-(tert-butoxycarbonyl)-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid (1.2 g, 2.6 mmole) in dry DMF (12 mL) under argon was treated with diisopropylethylamine (0.65 g, 5 mmole), EDC (0.764 g, 4 mmole) and HOBt · H_2O (0.54g, 4 mmole). The resulting solution was stirred for 10 min, then was treated with a solution of 3-aminopropionitrile fumarate in dry DMF (2 mL) containing diisopropylethylamine (0.85 g, 6.6 mmole). The reaction was stirred under argon for 18 hr, then was concentrated to dryness. The residue was partitioned between H_2O and EtOAc, and the layers were separated. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The oily residue was purified by silica gel flash chromatography (98:2 CH_2Cl_2/MeOH) to give the title compound (750 mg, 50%): MS (ES) 477.2 $[M+H]^+$.

d) (±)-1-(2-Cyanoethyl)-5-[[2,3,4,5-tetrahydro-7-(tert-butoxycarbonyl)-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepin-2-yl]methyl]tetrazole

A solution of (±)-2,3,4,5-tetrahydro-7-(tert-butoxycarbonyl)-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-[N-(2-cyanoethyl)acetamide] (750 mg, 1.3 mmole) in dry THF (15 mL) under argon was treated with triphenylphosphine (1.14 g, 4.6 mmole), trimethylsilylazide (0.52 g, 4.6 mmole), and diethylazodicarboxylate (0.8 mL, 4.6 mmole) at RT under argon. After 50 hr, the reaction was concentrated to dryness, and the residue was purified by silica gel flash chromatography (98.5:1.5 CH_2Cl_2/MeOH) to give the title compound (0.56g, 86%): MS (ES) m/e 502.2 $[M+H]^+$.

e) (±)-1-(2-Cyanoethyl)-5-[[2,3,4,5-tetrahydro-7-carboxy-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepin-2-yl]methyl]tetrazole

A solution of (±)-1-(2-cyanoethyl)-5-[[2,3,4,5-tetrahydro-7-(tert-butoxycarbonyl)-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepin-2-yl]methyl]tetrazole (0.5 g, 1 mmole) in CH_2Cl_2 (20 mL) at RT under argon was treated with 4 M HCl in dioxane (10 mL). After 20 hr, the reaction was concentrated to dryness, and the residue was diluted with 5% Na_2CO_3. The solution was extracted with EtOAc, and the EtOAc layer was discarded. The aqueous layer was acidified with dil HCl and extracted with EtOAc (3x). The combined EtOAc extracts were washed with brine, dried over $MgSO_4$ and evaporated to yield the title compound (0.36g, 81%): MS(ES) m/e 445.4 $[M+H]^+$.

f) (±)-1-(2-Cyanoethyl)-5-[[2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepin-2-yl]methyl]tetrazole

A solution of (±)-1-(2-cyanoethyl)-5-[[2,3,4,5-tetrahydro-7-carboxy-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepin-2-yl]methyl]tetrazole) (360 mg, 0.8 mmole) dry DMF (5 mL) was treated under argon with DIEA (129 mg, 1 mmole), EDC (172 mg, 0.9 mmole) and HOBt · H_2O (122 mg, 0.9 mmole). The reaction was stirred at RT for 10 min, then a solution of 2-aminomethylbenzimidazole dihydrochloride hydrate (352 mg, 1.6 mmole) in DMF (2 mL) containing DIEA (413 mg, 3.2 mmole) was added. After 20 hr, the reaction was concentrated to dryness and the residue was partitioned between H_2O and EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel flash chromatography (95:5 CH_2Cl_2/MeOH) to give the title compound (120 mg, 21%): MS (ES) m/e 575.2 $[M+H]^+$.

g) (±)-5-[[2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepin-2-yl]methyl]tetrazole

A solution of (±)-1-(2-cyanoethyl)-5-[[2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepin-2-yl]methyl]tetrazole (100 mg, 0.2 mmole) in MeOH (1 mL) was treated with thiophenol (0.02 mL) followed by 1 N NaOH solution (2.2 mL). After 3 hr, the reaction was concentrated to dryness, and the residue was purified by silica gel preparative TLC (85:15 CH_2Cl_2/MeOH). The isolated product was dissolved in H_2O,

and the solution was filtered to remove insoluble materials. The filtrate was treated with 2 drops of glacial AcOH. The precipitated solid was collected and dried to give the title compound (45 mg, 41%): MS (ES) m/e 522.2 $[M+H]^+$. Anal. Calcd for $C_{30}H_{31}N_9O_4 \cdot 2.25\ H_2O$: C, 56.15; H, 5.52; N,19.65. Found: C, 56.51; H, 5.05; N, 19.72.

Example 16

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-[4-[(2-carboxybenzoyl)amino]but-1-yl]-1H-1,4-benzodiazepine-2-acetic acid

a) N-[[2-(N-4-hydroxybut-1-yl)aminomethyl-4-tert-butoxycarbonyl]phenyl]-L-aspartic acid β-methyl ester

A mixture of N-[[2-formyl-4-tert-butoxycarbonyl]phenyl]-L-aspartic acid β-methyl ester (WO 95/18619; 2.55g, 7.26 mmol), 4Å molecular sieves, and 4-hydroxybutylamine (0.64 g, 7.26 mmol) in MeOH (35 mL) was stirred under argon at RT for 30 min, then sodium cyanoborohydride (0.49 g, 0.79 mmol) and acetic acid (0.3 mL) were added. The reaction mixture was kept at RT overnight and then the solvent was eliminated in vacuo. The residue was dissolved in H_2O and the solution was acidified to pH 4 with dil HCl. EtOAc extraction, drying ($MgSO_4$), filtration, and concentration gave the title compound (1.75 g, 57%) as a pale yellow solid: TLC R_f (4:20:20:56 MeOH/EtOAc/hexane/Cl_2CH_2) 0.22; ^1H NMR ($CDCl_3$) δ 1.55 (s, 9H), 1.56 (m, 2H), 1.80 (m, 2H), 3.01 (m, 4H), 3.55 (m, 2H), 3.70 (s, 3H), 4.05 (m, 1H), 4.40 (m, 1H), 4.55 (m, 1H), 6.81 (d, J = 8.4 Hz, 1H), 7.70 (s, 1H), 7.89 (d, J = 8.4 Hz, 1H).

b) Methyl (S)-7-(tert-butoxycarbonyl)-2,3,4,5-tetrahydro-3-oxo-4-(4-hydroxybut-1-yl)-1H-1,4-benzodiazepine-2-acetate

To a solution of N-[[2-(N-4-hydroxybut-1-yl)aminomethyl-4-tert-butoxycarbonyl]phenyl]-L-aspartic acid β-methyl ester (1.75 g, 4.1 mmol) and triethylamine (1.15 mL, 8.2 mmol) in dichloromethane (150 mL) under argon at RT was added benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (2.08 g, 14.7 mmol). The reaction mixture was stirred overnight at RT, then was washed sequentially with ice-cold dil HCl, water, 5% sodium bicarbonate, saturated brine, and then dried ($MgSO_4$). Filtration and concentration left a residue which was purified by silica gel flash column

chromatography (5% methanol:ethyl acetate) to give the title compound (0.631 g, 38%): TLC R_f (4% MeOH/EtOAc) 0.26; ^1H NMR ($CDCl_3$) δ 1.46-1.61 (m, 4H), 1.57 (s, 9H), 2.64 (d, J = 6.9 Hz, 1H), 2.66 (dd, J = 15.9, 6.3 Hz, 1H), 2.99 (dd, J = 15.6, 6.9 Hz, 1H), 3.56-3.54 (m, 4H), 3.74 (s, 3H), 3.84 (d, J = 16.2 Hz, 1H), 4.54 (m, 1H), 5.10 (m, 1H), 5.41 (d, J = 16.2 Hz, 1H), 6.49 (d, J = 8.3 Hz, 1H), 7.59 (d, J = 1.8 Hz, 1H), 7.67 (dd, J = 8.3, 1.8 Hz, 1H); MS (ES) m/e 407.2 $[M+H]^+$; $[\alpha]_D$ = -185.4° (c = 1, CH_3OH).

c) Methyl (S)-7-(tert-butoxycarbonyl)-2,3,4,5-tetrahydro-3-oxo-4-(4-phthalimidobut-1-yl)-1H-1,4-benzodiazepine-2-acetate

To a solution of methyl (S)-7-(tert-butoxycarbonyl)-2,3,4,5-tetrahydro-3-oxo-4-(4-hydroxybut-1-yl)-1H-1,4-benzodiazepine-2-acetate (437 mg, 1.07 mmol) and triphenylphosphine (308 mg, 1.17 mmol) in THF (20 mL) at RT under argon was sequentially added phthalimide (173 mg, 1.17 mmol) and diethyl azodicarboxylate (205 mg, 1.17 mmol). The reaction mixture was stirred overnight at RT, the solvent was removed, and the residue was purified by silica gel flash column chromatography (4:20:20:56 methanol/ethyl acetate/hexane/methylene chloride) to give the title compound (0.430 g, 75%): TLC R_f (4:20:20:56 MeOH/EtOAc/hexane/Cl_2CH_2) 0.32; ^1H NMR ($CDCl_3$) δ 1.55 (s, 9H), 1.55-1.61 (m, 4H), 2.68 (dd, J = 14.0, 5.7 Hz, 2H), 2.98 (dd, J = 14.0, 6.6 Hz, 1H), 3.46-3.64 (m, 4H), 3.71 (s, 3H), 3.85 (d, J = 16.5 Hz, 1H), 4.63 (d, J = 4.4 Hz, 1H), 5.08 (dd, J = 5.7, 6.6 Hz, 1H), 5.37 (d, J = 16.5 Hz, 1H), 6.48 (d, J = 8.3 Hz, 1H), 7.67 (s, 1H), 7.69 (d, J = 8.3, 1.8 Hz, 1H), 7.72-7.76 (m, 2H), 7.81-7.86 (m, 2H).

d) Methyl (S)-2,3,4,5-tetrahydro-7-carboxy-3-oxo-4-(4-phthalimidobutyl)-1H-1,4-benzodiazepine-2-acetate

To a solution of methyl (S)-7-(tert-butoxycarbonyl)-2,3,4,5-tetrahydro-3-oxo-4-(4-phthalimidobutyl)-1H-1,4-benzodiazepine-2-acetate (660 mg, 0.89 mmol) in dichloromethane (20 mL) was added 4 N HCl/dioxane (5 mL, 20 mmol) at RT under argon. The reaction mixture was stirred for 18 hr. The suspension was concentrated to give the title compound as an off-white solid (425 mg, 98%): ^1H NMR ($CDCl_3$) δ 1.55-1.61 (m, 4H), 2.71 (dd, J = 14.1, 6.0 Hz, 2H), 3.01 (dd, J = 14.1, 6.3 Hz, 1H), 3.50-3.65 (m, 4H), 3.75 (s, 3H), 3.89 (d, J = 16.5 Hz, 1H), 4.68 (d, J = 4.5 Hz, 1H), 5.12 (dd, J = 6.0, 6.3 Hz, 1H), 5.40 (d, J = 16.6 Hz, 1H), 6.41 (bs, 1H), 6.53 (d, J = 8.4 Hz, 1H), 7.69-7.75 (m, 4H) , 7.82-7.85 (m, 2H); MS (ES) m/e 480.2 $[M+H]^+$.

e) Methyl (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(4-phthalimidobut-1-yl)-1H-1,4-benzodiazepine-2-acetate

EDC (240 mg, 1.25 mmol) was added to a stirred solution of methyl (S)-2,3,4,5-tetrahydro-7-carboxy-3-oxo-4-(4-phthalimidobut-1-yl)-1H-1,4-benzodiazepine-2-acetate (0.85 g, 0.88 mmol), 2-(aminomethyl)benzimidazole dihydrochloride (230 mg, 1.04 mmol), HOBt ·H_2O (169 mg, 1.25 mmol), and diisopropylethylamine (0.78 mL, 4.5 mmol) in anhydrous acetonitrile (10 mL) at RT. After 19 h, the reaction was concentrated on the rotavap (high vacuum), and the residue was partitioned between H_2O (5 mL) and EtOAc (20 mL). The layers were separated and the organic layer was washed with H_2O (5 mL). Drying ($MgSO_4$), concentration, and silica gel chromatography (5% MeOH/CH_2Cl_2), gave the title compound (230 mg, 43%) as an off-white solid: TLC R_f (5% MeOH/Cl_2CH_2) 0.30; ^1H NMR (CD_3OD) δ 1.42-1.56 (m, 5H), 2.63 (dd, J = 6.4, 16.2 Hz, 1H), 2.95 (dd, J = 6.7, 16.2 Hz, 1H), 3.33-3.40 (m, 2H), 3.48-3.55 (m, 2H), 3.57 (d, J = 16.5 Hz, 1H), 3.67 (s, 3H), 4.72-4.80 (m, 3H), 5.03 (dd, J = 6.4, 6.7 Hz, 1H), 5.20 (d, J = 16.5 Hz, 1H), 6.44 (d, J = 8.4 Hz, 1H), 7.18-7.21 (m, 2H), 7.52-7.63 (m, 6H); 7.74-7.76 (m, 2H), 9.08 (br s, 1H).

f) (S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-[4-[(2-carboxybenzoyl)amino]but-1-yl]- 1H-1,4-benzodiazepine-2-acetic acid

LiOH (30 mg, 0.71 mmole) was added at RT to a solution of methyl (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(4-phthalimidobut-1-yl)-1H-1,4-benzodiazepine-2-acetate (223 mg, 0.33 mmol) in MeOH (2 mL) and H_2O(3 mL). The reaction mixture was stirred at RT for 19 hr. Acidification with dil HCl to pH 4 and concentration produced a solid. Filtration gave the title compound (145 mg, 66%) as a white solid: $[\alpha]_D$ = -100.4° (c = 1, CH_3OH); ^1H NMR (CD_3OD) δ 1.32-1.65 (m, 5H), 2.58 (dd, J = 16.4, 6.7 Hz, 1H), 2.90 (dd, J = 16.4, 7.9 Hz, 1H), 3.06 (m, 1H), 3.69 (m, 1H), 4.00 (d, J = 16.7 Hz, 1H), 4.69 (br s, 2H), 5.11 (dd, J = 7.9, 6.7 Hz, 1H), 5.36 (d, J = 16.7 Hz, 1H), 6.50 (d, J = 8.4 Hz, 1H), 7.29 (m, 2H), 7.37 (m, 4H); 7.51 (m, 2H), 7.664 (s, 1H), 7.74 (d, J = 6.8 Hz, 1H); MS (ES) m/e 613.2 $[M+H]^+$. Anal. Calcd for $C_{32}H_{32}N_6O_7$ ·1.5 H_2O: C, 60.08; H, 5.51; N, 113.14. Found: C, 59.77; H, 5.46; N, 12.98.

Example 17

Preparation of (±)-7-[3-(benzimidazol-2-yl)propyl]-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (±)-1-(tert-butoxycarbonyl)-7-(4-hydroxy-1-butyn-1-yl)-4-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzodiazepine-2-acetate

3-Butyn-1-ol (65 mg, 0.93 mmol), bis(triphenylphosphine)palladium (II) chloride (5 mg, 0.007 mmol), triphenylphosphine (10 mg, 0.038 mmol), and copper(I) iodide (10 mg, 0.052 mmol) were added under an Ar atmosphere to a solution of methyl (±)-2,3,4,5-tetrahydro-1-(tert-butoxycarbonyl)-7-iodo-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (obtained as in example 7c; 440 mg, 0.94 mmol) in triethylamine (34 mL). The reaction mixture was heated to reflux for 4 hr, then was filtered through celite®, and the filtrate was concentrated. The residue was purified by silica gel flash column chromatography (4:20:20:56 MeOH/EtOAc/hexane/Cl_2CH_2) to give the title compound (390 mg, 94%) as a pale yellow liquid: TLC R_f (5% MeOH: Cl_2CH_2) 0.37; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 1.8, 8.1 Hz, 1H), 7.31 (d, J = 1.8 Hz, 1H), 7.13 (d, J = 8.1 Hz, 1H), 5.15-5.23 (m, 1H), 4.75 (d, J = 14.4 Hz, 1H), 3.68 (d, J = 14.4 Hz, 1H), 3.63-3.67 (m, 2H), 3.59 (s, 3H), 3.04, (s, 3H), 2.88 (dd, J = 5.5, 15.2 Hz, 1H), 2.45 (t, J = 6.4 Hz, 2H), 2.26 (dd, J = 9.5, 15.2 Hz, 1H), 2.04 (br s, 1H), 1.34 (br s, 9H); MS (ES) m/e 417 $[M+H]^+$.

b) Methyl (±)-1-(tert-butoxycarbonyl)-7-(4-hydroxybut-1-yl)-4-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzodiazepine-2-acetate

10% Pd/C (40 mg) was added to a solution of methyl (±)-1-(tert-butoxycarbonyl)-7-(4-(hydroxy-1-butyn-1-yl)-4-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzodiazepine-2-acetate (370 mg, 0.89 mmol) in EtOH (20 mL), and the mixture was shaken on a Parr apparatus at RT under H_2 (50 psi). After 12 h, the reaction was filtered through celite®, and the filtrate was concentrated to afford the title compound (350 mg, 94%) as a pale yellow liquid: TLC R_f (4:20:20:56 MeOH/EtOAc/hexane/Cl_2CH_2) 0.55; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10-7.19 (m, 3H), 5.59-5.77 (m, 1H), 4.85 (d, J = 15.0 Hz, 1H), 3.68-3.60 (m, 5H), 3.12 (s, 3H), 2.85 (dd, J = 5.4, 15.3 Hz, 1H), 2.65 (t, J = 6.4 Hz, 2H), 2.34 (dd, J = 10.0, 15.3 Hz, 1H), 1.30-1.78 (m, 13H); MS (ES) m/e 421 $[M+H]^+$.

c) Methyl (±)-1-(tert-butoxycarbonyl)-7-(4-carboxybut-1-yl)-4-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzodiazepine-2-acetate

To a solution of methyl (±)-1-(tert-butoxycarbonyl)-7-(4-hydroxybut-1-yl)-4-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzodiazepine-2-acetate (350 mg, 0.82 mmol) in CH_2Cl_2 at 0°C was added 2,2,6,6-tetramethyl-oxopiperidinium chloride (*J. Org. Chem.* **1985**, *50*, 3930-3931; 220 mg, 1.1 mmol). The mixture was stirred for 2 hr at 0°C under Ar atmosphere. 2-Methyl-2-butene (1 mL) was added, followed by the addition of a freshly prepared solution of $NaClO_2$ (0.76 g, 6.7 mmol), $NaH_2PO_4 \cdot H_2O$ (0.78 g, 5.68 mmol) and H_2O (25 mL). The cooling bath was removed, and the mixture was taken up in EtOAc and washed successively with 0.05 M HCl and brine. Drying ($MgSO_4$), concentration, and silica gel chromatography (5% AcOH in 4:20:20:56 MeOH/EtOAc/hexane/Cl_2CH_2), gave the title compound (350 mg, 98%): TLC R_f (5% AcOH in 4:20:20:56 MeOH/EtOAc/hexane/Cl_2CH_2) 0.32; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13-7.18 (m, 3H), 5.60-5.69 (m, 1H), 4.83 (d, J = 14.2 Hz, 1H), 3.76 (d, J = 14.2 Hz, 1H), 3.66 (s, 3H), 3.12 (s, 3H), 2.93 (dd, J = 4.5, 15.3 Hz, 1H), 2.67 (t, J = 7.3 Hz, 2H), 2.36 (t, J = 7.3 Hz, 2H), 2.30-2.34 (m, 1H), 1.95 (q, J = 7.3 Hz, 2H), 1.34 (s, 9H); MS (ES) m/e 435 $[M+H]^+$.

d) Methyl (±)-1-(tert-butoxycarbonyl)-7-[3-(benzimidazol-2-yl)propyl]-4-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzodiazepine-2-acetate

To a stirred and cooled (-10°C) mixture of methyl (±)-1-(tert-butoxycarbonyl)-7-(4-carboxybut-1-yl)-4-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzodiazepine-2-acetate (350 mg, 0.8 mmol) and Et_3N (81 mg, 0.8 mmol) in anhydrous THF (8 mL) was added isobutylchloroformate (97 mg, 0.8 mmol). After 10 min, a solution of 1,2-phenylenediamine (1.43 g, 0.9 mmol) in THF (2 mL) was added. Stirring was continued at RT overnight, then the solvents were evaporated. The residue was dissolved in EtOAc, and the solution was washed sequentially with aqueous $NaHCO_3$ and brine. Drying ($MgSO_4$) and concentration produced a pale yellow solid. This was dissolved in glacial AcOH (5 mL), and the reaction was heated to 60°C. After 3 hr, the mixture was cooled, concentrated, neutralized with 2.5 N NaOH, and extracted with CH_2Cl_2. Drying ($MgSO_4$), concentration, and silica gel chromatography (gradient 1-5% MeOH/CH_2Cl_2) gave the title compound (200 mg, 50%): TLC R_f (4:20:20:56 MeOH/EtOAc/hexane/Cl_2CH_2) 0.18; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57-7.61 (m, 2H), 7.15-7.28 (m, 4H), 7.08 (s, 1H), 5.60-5.55 (m, 1H), 4.75-4.88 (m, 1H), 3.71 (d, J = 14.2 Hz, 1H), 3.70 (s, 3H), 3.10 (s, 3H), 2.94 (dd, J = 4.2, 15.3 Hz, 1H), 2.85-2.90 (m, 2H), 2.73-2.79 (m, 2H), 2.32-2.36 (m, 1H), 2.15-2.23 (m, 1H), 1.34 and 1.55 (br s, rotamers, 9H); MS (ES) m/e 507 $[M+H]^+$.

e) (±)-7-[3-(Benzimidazol-2-yl)propyl]-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetic acid

LiOH (17 mg, 0.71 mmole) was added at RT to a solution of methyl (±)-1-(tert-butoxycarbonyl)-7-[3-(benzimidazol-2-yl)propyl]-4-methyl-3-oxo-2,3,4,5-tetrahydro-1,4-benzodiazepine-2-acetate (200 mg, 0.395 mmol) in MeOH (2 mL) and H_2O (3 mL). The reaction mixture was stirred at RT for 4 hr. Acidification with dil HCl to pH 4 and concentration produced a white solid. This was dissolved in a mixture of methylene chloride (10 mL) and trifluoroacetic acid (5 mL) at 0°C, and the reaction was kept at 0°C for 30 min. The solvents were evaporated and the residue was triturated with ether and purified by ODS flash chromatography (gradient 10 to 18% CH_3CN/H_2O containing 0.1% TFA). Concentration and lyophilization gave the title compound (75 mg, 48%) as a colorless powder: ^1H NMR ((400 MHz, $CDCl_3$) δ 7.58-7.61 (m, 2H), 7.37-7.39 (m, 2H), 6.79 (d, J = 8.2 Hz, 1H), 6.68 (s, 1H), 6.39 (d, J = 8.2 Hz, 1H), 5.18(d, J = 16.8 Hz, 1H), 4.77 (dd, J = 7.0, 7.5 Hz, 1H), 3.63 (d, J = 16.8 Hz, 1H), 3.03-3.19 (m, 3H), 2.97 (s, 3H), 2.83 (dd, J = 7.0, 16.4 Hz, 1H), 2.52-2.56 (m, 2H), 2.08-2.12 (m, 2H); MS (ES) m/e 393.0 $[M+H]^+$. Anal. Calcd for $C_{22}H_{24}N_4O_3 \cdot C_2HF_3O2 \cdot 0.5\ H_2O$: C, 55.92; H, 5.08; N, 10.89. Found: C, 56.16; H, 4.92; N, 10.88.

Example 18

Preparation of (S)-2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) 4-[(Benzimidazol-2-yl)methyl]aminobutyronitrile

To a stirred mixture of 2-aminomethylbenzimidazole dihydrochloride (0.5 g, 2.2717 mmol) and $NaHCO_3$ (0.67 g, 7.951 mmol) in dry DMF (10 mL) was added 4-bromobutyronitrile (0.37 g, 2.4989 mmol). After stirring at RT for 24 hr, the mixture was concentrated. The residue was taken up in H_2O and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, concentrated , and purified by silica gel flash column chromatography (5% MeOH/CH_2Cl_2)to give the title compound (0.15 g, 35%) as a brown oil: ^1H NMR (250 MHz, DMSO-d_6) δ 1.82 (m, 2H), 2.45 (t, J = 4 Hz, 2H), 2.85 (t, J = 4 Hz, 2H), 4.11 (s, 2H), 7.14 (m, 2H), 7.50 (m, 2H).

b) Methyl (S)-2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-cyanopropyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

To a stirred mixture of 4-[(benzimidazol-2-yl)methyl]aminobutyronitrile (0.159 g, 0.7422 mmol), methyl 2,3,4,5-tetrahydro-7-carboxy-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.217 g, 0.7422 mmol), HOBt · H_2O (0.120 g, 0.8906 mmol), and i-Pr_2NEt (0.192 g, 1.4844 mmol) in dry CH_3CN (7 mL) was added EDC (0.265 g, 0.8906 mmol). After stirring at RT for 48 hr, the mixture was concentrated. The residue was taken up in H_2O and extracted with CH_2Cl_2. The organic layer was washed sequentially with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give a brown oil. Silica gel flash column chromatography (3% MeOH/CH_2Cl_2) gave the title compound (0.261 g, 74%) as an off white foam: ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.95 (m, 2H), 2.66 (dd, J = 16.4, 3.5 Hz, 1H), 2.78 (dd, J = 16.4, 3.5 Hz, 1H), 2.85 (t, J = 8.7 Hz, 2H), 3.45 (t, J = 8.7 Hz, 2H), 3.60 (s, 3H), 3.80 (d, J = 16 Hz, 1H), 4.52 (s, 2H), 4.84 (d, J = 2.9 Hz, 2H), 5.15 (m, 1H), 5.48 (d, J = 16 Hz, 1H), 6.40 (d, J = 3.5 Hz, 1H), 6.54 (d, J = 8.3 Hz, 1H), 7.25 (m, 4H);,7.50 (m, 1H), 7.62 (m, 1H).

c) (S)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-cyanopropyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

To a stirred solution of methyl (S)- 2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-cyanopropyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.261 g, 0.5478 mmol) in MeOH (5 mL) was added 2.5 N NaOH (0.7 mL, 1.6433 mmol). After stirring at RT overnight, the mixture was concentrated. The residue was taken up in H_2O, and the solution was acidified with 6 N HCl to pH = 4. The white solid was filtered and dried to afford the title compound (0.21 g , 81%): ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.95 (m, 2H), 2.66 (dd, J = 16.4, 3.5 Hz, 1H), 2.78 (dd, J = 16.4, 3.5 Hz, 1H), 2.85 (t, J = 8.7 Hz, 2H), 3.45 (t, J = 8.7 Hz, 2H), 3.80 (d, J = 16 Hz, 1H), 4.52 (s, 2H), 4.84 (d, J = 2.9 Hz, 2H), 5.15 (m, 1H), 5.48 (d, J = 16 Hz, 1H), 6.40 (d, J = 3.5 Hz, 1H), 6.54 (d, J = 8.3 Hz, 1H), 7.25 (m, 4H), 7.50 (m, 1H), 7.62 (m, 1H).

d) (S)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

A mixture of (S)-2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-cyanopropyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid (0.200 g, 0.4325 mmol) and NH_4OH (1 mL, 30% solution) in MeOH (5 mL) was hydrogenated over Ra/Ni at RT for 24 hr. The catalyst was filtered off, and the

filtrate was concentrated and purified by reverse phase chromatography (10% CH_3CN/H_2O containing 0.1% TFA) to give the title compound (0.100 g, 33%) as an off white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.45 (m, 2H), 1.72 (m, 2H), 2.54 (dd, J = 16.4, 3.5 Hz, 1H), 2.70 (m, 2H), 2.75 (dd, J = 16.4, 3.5 Hz, 1H), 2.95 (s, 3H), 3.65 (t, J = 8.7 Hz, 2H), 3.85 (d, J = 16 Hz, 1H), 5.05 (s, 2H), 5.15 (m, 1H), 5.48 (d, J = 16 Hz, 1H), 6.65 (d, J = 8.3 Hz, 1H), 7.20 (m, 2H), 7.61 (m, 2H), 7.75 (s, 2H), 7.85 (m, 2H); IR (KBr) 3425, 3000, 3100, 1728, 1675, 1630, 1625, 1613 cm^{-1}; MS (ES) m/e 479 (M+H). Anal. Calcd for $C_{25}H_{30}N_6O_4 \cdot 2\ CF_3CO_2H$: C, 49.30; H, 4.56; N,11.89. Found: C, 49.22; H, 4.89; N, 11.84.

Example 19

Preparation of (S)-2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl-N-(2-cyanomethyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) [(Benzimidazol-2-yl)methyl]aminoacetonitrile

Following the procedure of Example in 18(a), except substituting bromoacetonitrile for the 4-bromobutyronitrile, the title compound was prepared as an off white solid (0.15 g, 35%): ^{1}H NMR (250 MHz, DMSO-d_6): δ 3.71 (s, 2H), 3.98 (s, 2H), 7.14 (m, 2H), 7.50 (m, 2H).

b) Methyl (S)-2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl-N-(2-cyanomethyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Following the procedure of Example 18(b), except substituting [(benzimidazol-2-yl)methyl]aminoacetonitrile for 4-[(benzimidazol-2-yl)methyl]aminobutyronitrile, the title compound was prepared as an off white foam (0.487 g, 66%): ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.66 (dd, J = 16.4, 3.5 Hz, 1H), 2.78 (dd, J = 16.4, 3.5 Hz, 1H), 2.92 (s, 2H), 3.60 (s, 3H), 3.80 (d, J = 16 Hz, 1H), 4.52 (s, 2H), 4.84 (d, J = 2.9 Hz, 2H), 5.15 (m, 1H), 5.48 (d, J = 16 Hz, 1H), 6.40 (d, J = 3.5 Hz, 1H), 6.54 (d, J = 8.3 Hz, 1H), 7.25 (m, 4H), 7.50 (m, 2H), 7.62 (m, 2H).

c) (S)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl-N-(2-cyanomethyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure in Example 18(c), methyl (S)-2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl-N-(2-cyanomethyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate was saponified, and the product was recrystallized from EtOH, to give the title compound as a white solid (0.420 g,

89%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.66 (dd, J = 16.4, 3.5 Hz, 1H), 2.78 (dd, J = 16.4, 3.5 Hz, 1H), 2.92 (s, 2H), 3.80 (d, J = 16 Hz, 1H), 4.52 (s, 2H), 4.84 (d, J = 2.9 Hz, 2H), 5.15 (m, 1H), 5.48 (d, J = 16 Hz, 1H), 6.40 (d, J = 3.5 Hz, 1H), 6.54 (d, J = 8.3 Hz, 1H), 7.25 (m, 4H), 7.50 (m, 1H), 7.62 (m, 1H); MS (ES) m/e 465 $(M+H)^+$. Anal. Calcd for $C_{23}H_{22}N_6O_4 \cdot 2$ HCl: C, 53.19; H, 4.66; N, 16.18; Found: C, 52.98; H, 4.43; N, 16.53.

Example 20

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[benzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) Dimethyl (R)-2-trifluoromethanesulfonylsuccinate

To a stirred, cooled (0°C) mixture of dimethyl D-malate (5.5 g, 33.9213 mmol), and dry pyridine (2.82 g, 35.7164 mmol) in dry CH_2Cl_2 (55 mL) was added trifluoromethanesulfonic anhydride (10.0 g, 35.7164 mmol) dropwise. After stirring at 0°C for 4 hr, the mixture was quenched with H_2O and the layers were separated. The organic layer was washed sequentially with dil HCl and brine, dried over $MgSO_4$, and concentrated to give title compound (8.50 g, 96%) as a white solid: ^{1}H NMR(250 MHz, $CDCl_3$: δ 3.10 (d, J = 5.8 Hz, 2H), 3.74 (s, 3H), 3.78 (s, 3H), 5.52 (t, J = 5.8 Hz, 1H).

b) Dimethyl D-(2-cyanophenyl)malate

A mixture of 2-aminobenzonitrile (0.5 g, 4.2323 mmol), 2,6-di-tert-butylpyridine (0.85 g, 4.4439 mmol), and dimethyl (R)-2-trifluoromethanesulfonylsuccinate in 2:1 hexane/chloroform (25 mL) was stirred at RT for 76 hr. The mixture was concentrated, and the residue was taken up in H_2O and extracted with EtOAc. The organic extracts were washed sequentially with 10% HCl and brine, dried over $MgSO_4$, concentrated, and purified by silica gel flash column chromatography (10% EtOAc/hexane) to give the title compound (0.886 g, 80%) as a yellow solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.95 (d, J = 5.8 Hz, 1H), 3.74 (s, 3H), 3.78 (s, 3H), 4.60 (m, 1H), 5.28 (d, J = 5.8 Hz, 1H), 6.73 (d, J = 8.5 Hz, 1H), 6.80 (t, J = 8.5 Hz, 1H), 7.47 (m, 2H).

c) Methyl (S)-2,3,4,5-tetrahydro-3-oxo-1H-1,4-benzodiazepine-2-acetate

A solution of dimethyl D-(2-cyanophenyl)malate (10.75 g, 41.0006 mmol) in MeOH (pre-saturated with NH_3 (g) for 10 min, 100 mL) was hydrogenated over

Ra/Ni at 55 psi for 48 hr. The catalyst was filtered off, and the filtrate was concentrated and purified by silica gel flash column chromatography (40% EtOAc/hexane) to give the title compound (5.03 g, 53%) as an off white solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.65 (dd, J = 16.3, 7.6 Hz, 1H), 2.99 (dd, 16.3, 5.9 Hz, 1H), 3.74 (s, 3H), 3.95 (dd, J = 16, 6.9 Hz, 1H), 4.79 (m, 1H), 4.95 (dd, J = 16, 5.3 Hz, 1H), 6.55 (t, J = 5.3 Hz, 1H), 6.65 (d, J = 7.6 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H).

d) Methyl (S)-2,3,4,5-tetrahydro-7-bromo-3-oxo-1H-1,4-benzodiazepine-2-acetate

A mixture of methyl (S)-2,3,4,5-tetrahydro-3-oxo-1H-1,4-benzodiazepine-2-acetate (5.03 g, 21.4746 mmol) and n-Bu_4NBr3 (10.35 g, 21.4746 mmol) in $CHCl_3$ (100 mL) was stirred at RT for 3 hr, then the mixture was concentrated. The residue was taken up in H_2O, stirred, and filtered to afford the title compound (5.61 g, 83%) as an off white solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.74 (dd, J = 16.3, 7.6 Hz, 1H), 3.05 (dd, J = 16.3, 5.9 Hz, 1H), 3.75 (s, 3H), 4.05 (dd, J = 16, 6.9 Hz, 1H), 4.73 (t, J = 5.9 Hz, 1H), 4.86 (dd, J = 16, 5.3 Hz, 1H), 6.68 (d, J = 7.6 Hz, 1H), 6.75 (t, J = 5.3 Hz, 1H), 7.14 (s, 1H), 7.25 (d, J = 7.6 Hz, 1H).

e) Methyl (S)-2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate

A mixture of methyl (S)-2,3,4,5-tetrahydro-7-bromo-3-oxo-1H-1,4-benzodiazepine-2-acetate (1.5 g, 4.77905 mmol), 2-(methylaminomethyl)benzimidazole dihydrochloride (2.24 g, 9.5809 mmol), triphenylphosphine (1.26 g, 4.7905 mmol), n-Bu_3N (6.21 g, 33.5333 mmol), and $(Ph_3P)_4Pd$ (1.10 g, 0.9581 mmol) in N-methyl 2-pyrrolidinone (20 mL) was flushed with argon and carbon monoxide for 10 min. The mixture was then heated at 100-105°C under a carbon monoxide balloon for 8 hr. The mixture was cooled and acidified with 6 N HCl to pH = 2. The solution was extracted with EtOAc, and the EtOAc layer was discarded. The aqueous layer was neutralized with 30% NaOH and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, concentrated, and purified by silica gel flash column chromatography (5% MeOH/CH_2Cl_2) to give the title compound (1.62 g, 80%) as an off white solid: ^{1}H NMR (250 MHz, DMSO-d_6): δ 2.65 (dd, J = 16.3, 7.6 Hz, 1H), 2.81 (dd, J = 16.3, 5.9 Hz, 1H), 3.05 (s, 3H), 3.60(s, 3H), 3.75 (dd, J = 16.3, 6.9 Hz, 1H), 4.78 (s, 2H), 4.95 (m , 1H), 5.05 (dd, J = 16, 5.3 Hz, 1H), 6.20 (d, J = 5.9 Hz, 1H), 6.55 (d, J = 7.6 Hz, 1H), 7.25 (m, 4H), 7.55 (m, 2H), 8.21 (t, J = 5.3 Hz, 1H).

f) (S)-2,3,4,5-Tetrahydro-7-[[[benzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure of Example 18(c), methyl (S)-2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate was saponified to afford the title compound (0.060 g, 57%) as an off white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.52 (dd, J = 16.3, 7.6 Hz, 1H), 2.84 (dd, J = 16.3, 5.9 Hz, 1H), 3.20 (s, 3H), 3.75 (dd, J = 16.3, 6.9 Hz, 1H), 4.95 (t, J = 5.9 Hz, 1H), 5.05 (dd, J = 16, 5.3 Hz, 1H), 5.10 (s, 2H), 6.59 (d, J = 7.6 Hz, 1H), 7.12 (s, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.48 (m , 2H), 7.69 (m, 2H), 7.90 (d, J = 5.3 Hz, 1H); IR (KBr) 3600-3100, 3100-2800, 1681, 1613, 1601, 1485, 1445, 1314, 830, 764, 742 cm^{-1}; MS (ES) m/e 422 $(M+H)^+$. Anal. Calcd for $C_{21}H_{21}N_5O_4$: C, 61.91; H, 5.20; N, 17.19. Found: C, 61.57; H, 5.32; N, 17.29.

Example 21

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[[1-(2-hydroxyethyl)benzimidazol-2-yl]methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) Ethyl 2-[[(benzimidazol-2-yl)methyl]amino]acetate

A mixture of 2-aminomethylbenzimidazole dihydrochloride hydrate (4.0 g, 18.1736 mmol), $NaHCO_3$ (7.63 g, 90.868 mmol), and ethyl 2-bromoacetate (4.55 g, 27.2603 mmol) in dry DMF (60 mL) was stirred at RT for 24 hr, then was concentrated. The residue was taken up in H_2O and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, concentrated, and purified by silica gel flash column chromatography (5% MeOH/CH_2Cl_2) to give the title compound (0.50 g, 12%) as a brown oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.95 (s, 3H), 3.48 (s, 2H), 4.50 (m, 4H), 7.25 (m, 2H), 7.35 (m, 1H), 7.73 (m, 1H).

b) Methyl (S)-2,3,4,5-tetrahydro-7-[[[[1-(2-acetyloxyethyl)benzimidazol-2-yl]methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Following the procedure of Example 18(b), except substituting ethyl 2-[[(benzimidazol-2-yl)methyl]amino]acetate for the 4-[(benzimidazol-2-yl)methyl]aminobutyronitrile, the title compound (0.251 g, 78.5%) was prepared as a white solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.95 (s, 3H), 2.66 (dd, J = 16.4, 3.5 Hz, 1H), 2.95 (s, 3H), 3.05 (dd, J = 16.4, 3.5 Hz, 1H), 3.60 (d, J = 16 Hz, 1H), 3.75 (s, 3H), 4.45(d, J = 5.9 Hz, 2H), 4.62 (s, 2H), 4.92 (t, J = 5.9 Hz, 2H), 5.10 (m, 1H),

5.40 (d, J = 16 Hz, 1H), 6.49 (d, J = 8.3 Hz, 1H), 7.32 (m, 3H), 7.60 (m, 2H), 7.71 (m, 1H), 8.15 (t, J = 5.3 Hz, 1H).

c) (S)-2.3,4,5-Tetrahydro-7-[[[[1-(2-hydroxyethyl)benzimidazol-2-yl]methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

To a stirred, partial suspension of methyl (S)-2.3,4,5-tetrahydro-7-[[[[1-(2-acetyloxyethyl)benzimidazol-2-yl]methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.241 g, 0.475 mmol) in THF (5 mL) was added 1.0 N LiOH (1.4 mL, 1.425 mmol). After stirring at RT overnight, the mixture was concentrated. The residue was taken up in H_2O and acidified with AcOH to pH = 4. The off-white solid was filtered and triturated with acetone to afford the title compound (0.16 g, 75%) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6):δ 2.54 (dd, J = 16.4, 3.5 Hz, 1H), 2.95 (s, 3H), 3.05 (dd, J = 16.4, 3.5 Hz, 1H), 3.60 (d, J = 16 Hz, 1H), 4.45 (d, J = 5.9 Hz, 2H), 4.62 (s, 2H), 4.92 (t, J = 5.9 Hz, 2H), 5.10 (m, 1H), 5.40 (d, J = 16 Hz, 1H), 6.49 (d, J = 8.3 Hz, 1H), 7.32 (m, 3H), 7.60 (m, 2H), 7.71 (m, 1H), 8.15 (t, J = 5.3 Hz, 1H); MS (ES) m/e 452 $(M+H)^+$. Anal. Calcd for $C_{23}H_{25}N_5O_5 \cdot 0.75\ H_2O$: C, 59.71; H, 5.72; N, 15.14. Found: C, 59.65, H, 5.70; N, 14.88.

Example 22

Preparation of (±)-2,3,4,5-tetrahydro-7-[[N-(benzimidazol-2-yl)methyl-N-[[4-(2-carboxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid

a) 4-[[(Benzimidazol-2-yl)methyl]amino]butylphthalimide

A mixture of 2-aminomethylbenzimidazole dihydrochloride hydrate (22.10 g, 100.7269 mmol), $NaHCO_3$ (42.40 g, 503.6347 mmol), and 4-bromobutylphthalimide (34.10 g, 120.8723 mmol) in dry DMF (250 mL) was heated at 100-110°C for 6 hr, then was cooled and concentrated. The residue was taken up in H_2O and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, concentrated, and purified by silica gel flash column chromatography (5% MeOH/CH_2Cl_2) to give the title compound (10.8 g, 31%) as a brown foam: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.65 (m, 2H), 1.85 (m, 2H), 2.75 (t, J = 8.9 Hz, 2H), 3.78 (t, J = 8.9 Hz, 2H), 4.17 (s, 2H), 7.20 (m, 2H), 7.60 (m, 2H), 7.72 (m, 2H), 7.88 (m, 2H).

b) Methyl (±)-2,3,4,5-tetrahydro-7-[[N-(benzimidazol-2-yl)methyl-N-[[4-(phthalimido)butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate

To a stirred mixture of 4-[[(benzimidazol-2-yl)methyl]amino]butylphthalimide (1.75 g, 5.0525 mmol), methyl (±)-2,3,4,5-tetrahydro-7-carboxy-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate (1.61 g, 4.2104 mmol), HOBt · H_2O (0.69 g, 5.0525 mmol), and i-Pr_2NEt (1.10 g, 8.4209 mmol) in dry CH_3CN (30 mL) was added EDC (1.50 g, 5.0525 mmol). After stirring at RT for 24 hr, the mixture was concentrated. The residue was taken up in H_2O and extracted with CH_2Cl_2. The organic extracts were washed sequentially with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, concentrated, and purified by silica gel flash column chromatography (5% MeOH/CH_2Cl_2) to give the title compound (2.85 g, 95%) as a yellow foam: ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.60 (m, 2H), 2.65 (m, 2H), 2.85 (dd, J = 16.4, 3.5 Hz, 1H), 3.55 (m, 4H), 3.65 (s, 3H), 4.00 (d, J= 16.0 Hz, 1H), 4.18 (q, J = 8.9 Hz, 2H), 4.75 (s, 2H), 5.15 (m, 1H), 5.45 (d, J = 16.0 Hz, 1H), 6.23 (d, J = 5.3 Hz, 1H), 6.57 (d, J = 7.6 Hz, 1H), 7.20 (m, 7H), 7.55 (m, 4H), 7.90 (m, 4H).

c) Methyl (±)-tetrahydro-7-[[N-[benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate

A mixture of methyl (±)-2,3,4,5-tetrahydro-7-[[N-(benzimidazol-2-yl)methyl-N-[[4-(phthalimido)butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate (0.50 g, 0.7015 mmol) and hydrazine (0.07 g, 2.1045 mmol) in MeOH (5 mL) was refluxed for 6 hr, then was cooled and concentrated. The residue was taken up in H_2O, acidified to pH = 2 with 6N HCl, and filtered to remove a white solid. This solid was discarded. The aqueous filtrate was extracted with EtOAc, and the EtOAc layer was discarded. The aqueous layer was basified to pH = 9 with Na_2CO_3 and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated to give the title compound (0.41 g, 89%) as an off white solid: ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.47 (m, 2H), 1.75 (m, 2H), 2.65 (m, 5H), 2.85 (dd, J = 16.3, 5.9 Hz, 1H), 3.65 (s, 7H), 4.05 (d, J = 16.0 Hz, 1H), 5.05 (s, 2H), 5.15 (m, 1H), 5.45 (d, J = 16, 1H), 6.65 (d, J = 7.6 Hz, 1H), 7.25 (m, 6H), 7.41 (s, 1H), 7.60 (m, 2H), 7.85 (m, 2H).

d) (±)-2,3,4,5-Tetrahydro-7-[[N-(benzimidazol-2-yl)methyl-N-[[4-(2-carboxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid

To a stirred solution of methyl (±)-tetrahydro-7-[[N-[benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate (0.34 g, 0.47 mmol) in THF was added 1.0 N LiOH (1.2 mL). After stirring at RT overnight, the mixture was concentrated, and the residue was acidified with AcOH to pH = 4. The solid was filtered and triturated with acetone/ether to give the title compound (0.130 g, 39%) as a white solid: ^{1}H NMR(400 MHz, DMSO-d_6) δ 1.47 (m, 2H), 1.75 (m, 2H), 2.54 (dd, J = 16.3, 3.5 Hz, 1H), 2.65 (m, 2H), 2.85 (dd, J = 16.3, 5.9 Hz, 1H), 3.20 (m, 2H), 3.75 (m, 4H), 4.05 (d, J = 16.0 Hz, 1H), 5.05 (s, 2H), 5.15 (m, 1H), 5.45 (d, J = 16, 1H), 6.65 (d, J = 7.6 Hz, 1H), 7.25 (m, 6H), 7.41 (s, 1H), 7.60 (m, 2H), 7.85 (m, 2H); IR (KBr) 3400, 3326, 3100-3000, 1721, 1637, 1626, 1616, 1607,1300, 750, 694 cm^{-1}; MS (ES) m/e 717 (M+H)$^+$. Anal. Calcd for $C_{40}H_{38}N_6O_8 \cdot 3\ H_2O$: C, 63.56; H, 5.87; N, 11.12. Found: C, 63.56; H, 5.83; N, 11.04.

Example 23

Preparation of (±)-2,3,4,5-tetrahydro-7-[[N-(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-2-hydroxybenzoyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (±)-2,3,4,5-tetrahydro-7-[[N-(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-2-hydroxybenzoyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate

To a mixture of methyl (±)-2,3,4,5-tetrahydro-7-[[N-(benzimidazol-2-yl)methyl-N-[[4-(phthalimido)butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate (0.409 g, 0.702 mmol), 4-azidosalicylic acid-N-hydroxysuccinimide ester (0.194 g, 0.702 mmol), and i-Pr_2NEt (0.272 g, 2.106 mmol) in dry 2:1 CH_3CN/DMF (10 mL) was added EDC (0.25 g, 0.8424 mmol). After stirring at RT for 24 hr, the mixture was concentrated. The residue was taken up in H_2O, stirred, and filtered to afford, after drying, the title compound (0.204 g, 39%) as an off white solid: ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.40 (m, 2H), 1.75 (m, 2H), 2.65 (m, 3H), 2.75 (dd, J = 16.3, 5.9 Hz, 1H), 3.20 (m, 2H), 3.51 (m, 4H), 3.65 (m, 3H), 3.95 (d, J = 16 Hz, 1H), 4.79 (s, 2H), 5.12 (m, 1H), 5.37 (d, J = 16 Hz, 1H),

6.20 (s, 1H), 6.55 (m, 3H), 7.20 (m, 8H), 7.55 (m, 3H), 7.85 (d, J = 7.6 Hz, 1H), 7.98 (s, 1H), 8.75 (s, 1H).

b) (±)-2,3,4,5-Tetrahydro-7-[[N-(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-2-hydroxybenzoyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure of Example 22(d), methyl (±)-2,3,4,5-tetrahydro-7-[[N-(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-2-hydroxybenzoyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate was saponified to afford the title compound (0.100 g, 50%) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.40 (m, 2H), 1.75 (m, 2H), 2.65 (m, 3H), 2.75 (dd, J = 16.3, 5.9 Hz, 1H), 3.20 (m, 2H), 3.51 (m, 4H), 3.95 (d, J = 16 Hz, 1H), 4.79 (s, 2H), 5.12 (m, 1H), 5.37 (d, J = 16 Hz, 1H), 6.20 (s, 1H), 6.55 (m, 3H), 7.20 (m, 8H), 7.55 (m, 3H), 7.85 (d, J = 7.6 Hz, 1H), 7.98 (s, 1H), 8.75 (s, 1H); MS (ES) m/e 730 $(M+H)^+$. Anal. Calcd for $C_{39}H_{39}N_9O_6 \cdot 2.5\ H_2O$: C, 60.46; H, 5.72; N, 16.27. Found: C, 60.46; H, 5.43; N, 15.90.

Example 24

Preparation of 2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl-N-[[[(+)-biotinoyl]amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-(2RS)-acetic acid

a) Methyl 2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl-N-[[[(+)-biotinoyl]amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-(2RS)-acetate

To a mixture of methyl (±)-tetrahydro-7-[[N-[benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate (0.40 g, 0.6865 mmol), (+)-biotin (0.17 g, 0.6865 mmol), HOBt · H_2O (0.11 g, 0.8239 mmol), and i-Pr_2NEt (0.18 g, 1.3730 mmol) in 1:2 DMF/CH_3CN (12 mL) was added EDC (0.25 g, 0.8239 mmol). After stirring at RT for 24 hr, the mixture was concentrated. The residue was taken up in H_2O and extracted with $CHCl_3$. The organic extracts were washed sequentially with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, concentrated, and purified by silica gel flash column chromatography (10% MeOH/CH_2Cl_2) to give the title compound (0.24 g, 44%) as a yellow foam: ^{1}H NMR (250 MHz, DMSO-d_6) δ 1.30 (m, 2H), 1.60 (m, 4H), 2.05 (t, J = 8.9 Hz, 2H);,2.60 (m, 3H), 2.68 (dd, J = 16.3, 5.9 Hz, 1H), 3.10 (m, 4H), 3.45 (m, 2H), 3.60

(m, 2H), 3.65 (s, 3H), 4.01 (d, J = 16 Hz, 1H), 4.12 (t, J = 8.9 Hz, 1H), 4.30 (t, J = 8.9 Hz, 1H), 4.78 (s, 2H), 5.10 (m, 1H), 5.45 (d, J = 16 Hz, 1H), 6.20 (d, J = 5.3 Hz, 1H), 6.40 (d, J = 8.9 Hz, 2H), 6.55 (d, J = 7.6 Hz, 1H), 7.25 (m, 9H), 7.45 (m, 1H), 7.55 (m, 1H), 7.70 (t, J = 8.6 Hz, 1H).

b) 2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl-N-[[[(+)-biotinoyl]amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-(2RS)-acetic acid

To a stirred solution of methyl 2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl-N-[[[(+)-biotinoyl]amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-(2RS)-acetate (0.24 g, 0.2967 mmol) in 1:2 THF/MeOH (6 mL) was added 1.0 N LiOH (0.44 mL). After stirring at RT overnight, the mixture was concentrated. The residue was taken up in H_2O and acidified with AcOH to pH = 4. The off-white solid was filtered, and triturated with hot acetone to give the title compound (0.160 g, 68%) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) d 1.30 (m, 2H), 1.60 (m, 4H), 2.05 (t, J = 8.9 Hz, 2H), 2.60 (m, 3H), 2.68 (dd, J = 16.3, 5.9 Hz, 1H), 3.10 (m, 4H), 3.45 (m, 2H), 3.60 (m, 2H), 4.01 (d, J = 16 Hz, 1H), 4.12 (t, J = 8.9 Hz, 1H), 4.30 (t, J = 8.9 Hz, 1H), 4.78 (s, 2H), 5.10 (m, 1H), 5.45 (d, J = 16 Hz, 1H), 6.20 (d, J = 5.3 Hz, 1H), 6.40 (d, J = 8.9 Hz, 2H), 6.55 (d, J = 7.6 Hz, 1H), 7.25 (m, 9H), 7.45 (m, 1H), 7.55 (m, 1H), 7.70 (t, J = 8.6 Hz, 1H); MS (ES) m/e 795 $(M+H)^+$. Anal. Calcd for $C_{42}H_{50}N_8O_6S \cdot 1.75\ H_2O$: C, 61.04; H, 6.52; N, 13.56. Found: C, 60.89; H, 6.24; N, 13.31.

Example 25

Preparation of (±)-2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid

a) (±)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure in Example 24(b), methyl (±)-2,3,4,5-tetrahydro-7-[[N-[benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetate was saponified to give the title compound (0.250 g, 80%) as an off white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.37 (m, 2H), 1.62 (m, 2H), 2.52 (dd, J = 3.5 Hz, 1H), 2.64 (m, 2H), 2.75 (dd, J =

16.3, 5.9 Hz, 1H), 3.51 (m, 4H), 3.91 (d, J = 16 Hz, 1H), 4.98 (s, 2H), 5.05 (m, 1H), 5.37 (d, J = 16 Hz, 1H), 6.53 (d, J = 7.9 Hz, 2H), 7.17 (m, 7H), 7.52 (m, 1H), 7.62 (s, 1H), 7.78 (m, 1H); IR (KBr): 3386, 3100-3000, 1647, 1613, 1403, 740, 699 cm^{-1}; MS (ES) m/e 569 $(M+H)^+$. Anal. Calcd for $C_{32}H_{36}N_6O_4 \cdot 2.75\ H_2O$: C, 62.18; H, 6.77; N, 13.60. Found: C, 62.11; H, 6.68; N, 13.57.

Example 26

Preparation of (±)-2,3,4,5-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-3-iodo-2-hydroxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid

a) 3-Iodo-4-azidosalicylic acid-N-hydroxysuccinimide ester

To a stirred mixture of 4-azidosalicylic acid N-hydroxysuccinimide ester (0.500 g, 1.8103 mmol) and silver trifluoroacetate (0.44 g, 1.9913 mmol) in $CHCl_3$ (10 mL) was added iodine (0.510 g, 1.9913 mmol). After stirring at RT overnight, the reaction was filtered to remove a solid precipitate. The filtrate was washed sequentially with H_2O, saturated $NaHCO_3$ and brine, then was dried over $MgSO_4$. Concentration gave the title compound (0.703 g, 97%) as a light purple solid: ^1H NMR (250 MHz, $CDCl_3$) δ 2.98 (s, 4H), 6.83 (d, J = 7.6 Hz, 1H), 8.05 (d, J = 7.6 Hz, 1H).

b) Methyl (±)-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-3-iodo-2-hydroxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1.4-benzodiazepine-2-acetate

Following the procedure in Example 22(b), except substituting 3-iodo-4-azidosalicylic acid-N-hydroxysuccinimide ester for the 4-[[(benzimidazol-2-yl)methyl]amino]butylphthalimide, the title compound (0.312 g, 56%) was prepared as a yellow foam: ^1H NMR (250 MHz, DMSO-d_6) δ 1.42 (m, 2H), 1.60 (m, 2H), 2.52 (dd, J = 16.3, 3.5 Hz, 1H), 2.63 (m, 2H), 2.79 (dd, J = 16.3, 5.9 Hz, 1H), 3.25 (s, 2H), 3.55 (m, 6H), 3.65 (s, 3H), 3.95 (d, J = 16 Hz, 1H), 4.75 (s, 2H), 5.02 (m, 1H), 5.35 (d, J = 16 Hz, 1H), 6.14 (d, J = 5.3 Hz, 1H), 6.52 (d, J = 7.9 Hz, 1H), 6.86 (d, J = 7.9 Hz, 1H), 7.25 (m, 10H), 7.51 (s, 2H), 7.90 (d, J = 7.9 Hz, 1H), 9.01 (s, 1H).

c) (±)-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-3-iodo-2-hydroxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1.4-benzodiazepine-2-acetic acid

Following the procedure in Example 22(c), methyl (±)-tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-3-iodo-2-hydroxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1.4-benzodiazepine-2-acetate was saponified. Purification by silica gel flash column chromatography (0.5, 0.5, 9.5 AcOH/MeOH/CH_2Cl_2) gave the title compound (0.170 g, 58%) as an off white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.42 (m, 2H), 1.60 (m, 2H), 2.52 (dd, J = 16.3, 3.5 Hz, 1H), 2.63 (m, 2H), 2.79 (dd, J = 16.3, 5.9 Hz, 1H), 3.25 (s, 2H), 3.55 (m, 6H), 3.95 (d, 16, 1H), 4.75 (s, 2H), 5.02 (m, 1H), 5.35 (d, J = 16 Hz, 1H), 6.14 (d, J = 5.3 Hz, 1H), 6.52 (d, J = 7.9 Hz, 1H), 6.86 (d, J = 7.9 Hz, 1H), 7.25 (m, 10H), 7.51 (s, 2H), 7.90 (d, J = 7.9 Hz, 1H), 9.01 (s, 1H); MS (ES) m/e 856 $(M+H)^+$; IR (KBr): 3360, 3100-3000, 2116, 1704, 1643, 1610, 1586, 1477, 1305, 1274, 766, 700 cm^{-1}. Anal. Calcd for $C_{39}H_{38}IN_9O_6 \cdot 4.5\ H_2O$: C, 50.01; H, 5.06; N, 13.46. Found: C, 50.19; H, 5.01; N, 13.12.

Example 27

Preparation of 5-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-benzimidazole-2-aminoacetic acid

a) Methyl 5-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-benzimidazole-2-aminoacetate

Diisopropylethylamine (1.1 mL, 6.48 mmol) was added to a stirred solution of methyl 5-carboxy-benzimidazole-2-aminoacetate (0.24 g, 0.96 mmol), 2-(methylaminomethyl)benzimidazole bis-trifluoroacetate (0.56 g, 1.44 mmol), HOBt · H_2O (0.19 g, 1.44 mmol), and EDC (0.28 g, 1.44 mmol) in anhydrous DMF (8 mL) at RT. After 23 h, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed sequentially with 5% $NaHCO_3$ (30 mL) and brine (30 mL). Drying ($MgSO_4$), concentration, and silica gel chromatography (10% MeOH/CH_2Cl_2) gave the title compound (0.16 g, 42%) as an off-white solid: MS (ES) m/e 393.0 $(M+H)^+$.

b) 5-[[[(Benzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-benzimidazole-2-aminoacetic acid

1.0 N LiOH (1.0 mL, 1.0 mmol) was added dropwise at RT to a mixture of methyl 5-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-benzimidazole-2-aminoacetate (0.16 g, 0.41 mmol) in THF (10 mL) and H_2O (10 mL). After 1 h, the reaction mixture was concentrated to a small volume on the rotavap and cooled in an ice bath before neutralizing with 1.0 N AcOH (1.0 mL). The solid was collected, washed with cold H_2O, and air dried to give the title compound (0.15 g, 100%) as an off white solid: MS (ES) m/e 379.2 $(M+H)^+$.

Example 28

Preparation of (±)-2,3,4,5-Tetrahydro 7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (±)-2,3,4,5-tetrahydro 7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetate

Diisopropylethylamine (0.94 mL, 5.4 mmol) was added to a stirred solution of methyl (±)-7-carboxy-4-(3,3-dimethylbutyl)-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetic acid (0.39 g, 1.08 mmol), 2-(methylaminomethyl)benzimidazole bis(trifluoroacetate) (0.42 g, 1.08 mmol),), HOBt · H_2O (0.22 g, 1.62 mmol), and EDC (0.31 g, 1.62 mmol) in anhydrous DMF (8 mL) at RT. After 23 h, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed sequentially with 5% $NaHCO_3$ (2 x 25 mL) and brine (25 mL). Drying ($MgSO_4$), concentration, and silica gel chromatography (7% MeOH/CH_2Cl_2) gave the title compound (0.39 g, 71%) as a white solid: MS (ES) m/e 506.4 $(M+H)^+$.

b) (±)-2,3,4,5-Tetrahydro 7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

1.0 N LiOH (1.0 mL, 1.0 mmol) was added dropwise at RT to a mixture of methyl (±)-2,3,4,5-tetrahydro 7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.38 g, 0.75 mmol) in THF (10 mL) and H_2O (10 mL). After 50 min, the reaction mixture was concentrated to a small volume on the rotavap and cooled in an ice bath before neutralizing with 1.0 N AcOH (2.5 mL). The solid was collected, washed with a cold H_2O, and air dried to give the title compound (0.27 g, 73%) as a white solid: MS (ES) m/e 492.2 $(M+H)^+$.

Example 29

Preparation (±)-2,3,4,5-Tetrahydro 7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (±)-2,3,4,5-tetrahydro 7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetate

Diisopropylethylamine (0.79 mL, 4.56 mmol) was added to a stirred solution of methyl (±)-7-carboxy-4-(3,3-dimethylbutyl)-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetic acid (0.33 g, 0.91 mmol), 2-(aminomethyl)benzimidazole dihydrochloride hydrate (0.3 g, 1.36 mmol), HOBt · H_2O (0.18 g, 1.36 mmol), and EDC (0.26 g, 1.36 mmol) in anhydrous DMF (8 mL) at RT. After 20 h, the reaction mixture was diluted with CH_2Cl_2 (70 mL) and washed sequentially with 5% $NaHCO_3$ (2 x 20 mL) and brine (20 mL). Drying ($MgSO_4$), concentration, and silica gel chromatography (7% MeOH/CH_2Cl_2) gave the title compound (0.25 g, 56%) as a white solid: MS (ES) m/e 492.4 $(M+H)^+$.

b) (±)-2,3,4,5-Tetrahydro 7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

1.0 N LiOH (1.0 mL, 1.0 mmol) was added dropwise at RT to a mixture of methyl (±)-2,3,4,5-tetrahydro 7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.24 g, 0.49 mmol) in THF (8 mL) and H_2O (8 mL). After 2.5 h, the reaction mixture was concentrated to a small volume on the rotavap and cooled in an ice bath before neutralizing with 1.0 N AcOH (1.2 mL). The solid was collected, washed with cold H_2O ,and air dried to give the title compound (0.25 g, 109%) as a white solid: MS (ES) m/e 478.2 $(M+H)^+$.

Example 30

Preparation of (±)-2,3,4,5-Tetrahydro 7-[[[(4-azabenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (±)-2,3,4,5-tetrahydro 7-[[[(4-azabenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetate

Diisopropylethylamine (0.53 mL, 3.0 mmol) was added to a stirred solution of methyl (±)-7-carboxy-4-(3,3-dimethylbutyl)-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetic acid (0.22 g, 0.61 mmol), 2-(methylamino)methyl-4-azabenzimidazole diacetate (0.29 g, 1.0 mmol), HOBt · H_2O (0.12 g, 0.91 mmol), and EDC (0.17 g, 0.91 mmol) in anhydrous CH_3CN (12 mL) at RT. After 21 h, the reaction mixture was concentrated, diluted with CH_2Cl_2 (100 mL), and washed sequentially with 5% $NaHCO_3$ (2 x 20 mL) and brine (20 mL). Drying ($MgSO_4$), concentration, and silica gel chromatography (7% MeOH/CH_2Cl_2) gave the title compound (0.147 g, 48%) as a white solid: MS (ES) m/e 507.4 $(M+H)^+$.

b) (±)-2,3,4,5-Tetrahydro 7-[[[(4-azabenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

1.0 N LiOH (0.69 mL, 0.69 mmol) was added dropwise at RT to a mixture of methyl (±)-2,3,4,5-tetrahydro 7-[[[(4-azabenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.14 g, 0.276 mmol) in THF (8 mL) and H_2O (8 mL). After 2 h, the reaction mixture was concentrated to a small volume on the rotavap and cooled in an ice bath before neutralizing with 1.0 N AcOH (0.69 mL). The solid was collected, washed with cold H_2O, and air dried to give the title compound (0.074 g, 54%) as a white solid: MS (ES) m/e 493.2 $(M+H)^+$.

Example 31

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[[1-[(benzimidazol-2-yl)methyl]benzimidazol-2-yl]methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (S)-2,3,4,5-tetrahydro-7-[[[[1-[(benzimidazol-2-yl)methyl]benzimidazol-2-yl]methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Diisopropylethylamine (0.27 mL, 1.53 mmol) was added to a stirred solution of methyl (S)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate trifluoroacetate (0.14 g, 0.34 mmol), 2-[[1-[(benzimidazol-2-yl)methyl]benzimidazole]methyl]amine bis(trifluoroacetate) (0.17 g, 0.34 mmol),

HOBt · H_2O (0.064 g, 0.48 mmol), and EDC (0.091 g, 0.48 mmol) in anhydrous DMF (10 mL) at RT. After 22 h, the reaction mixture was concentrated, diluted with CH_2Cl_2 (70 mL), and washed sequentially with 5% $NaHCO_3$ (2x30 mL) and brine (20 mL). Drying ($MgSO_4$), concentration, and silica gel chromatography (7% MeOH/CH_2Cl_2) gave the title compound (0.080 g, 43%) as a white solid: MS (ES) m/e 552.2 $(M+H)^+$.

b) (S)-2,3,4,5-Tetrahydro-7-[[[[1-[(benzimidazol-2-yl)methyl]benzimidazol-2-yl]methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

1.0 N LiOH (0.36 mL, 0.36 mmol) was added dropwise at RT to a mixture of methyl (S)-2,3,4,5-tetrahydro-7-[[[[1-[(benzimidazol-2-yl)methyl]benzimidazol-2-yl]methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.08 g, 0.14 mmol) in THF (5 mL) and H_2O (4 mL). After 2 h, the reaction mixture was concentrated to a small volume on the rotavap and cooled in an ice bath before neutralizing with 1.0 N AcOH (0.69 mL). The solution was lyophilized to a crude product (0.086 g) as a white powder. Purification on C-18 Bond Elute (0%-20% CH_3CN/H_2O containing 0.1% TFA) afforded the title compound as a white powder: MS (ES) m/e 538.2 $(M+H)^+$.

Example 32

Preparation of (S)-2,3,4,5-Tetrahydro-7-[[bis[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (S)-2,3,4,5-tetrahydro-7-[[bis[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Diisopropylethylamine (0.22 mL, 1.29 mmol) was added to a stirred solution of methyl (S)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate trifluoroacetate (0.075 g, 0.26 mmol), bis[(benzimidazol-2-yl)methyl]amine tris(trifluoroacetate) (0.16 g, 0.26 mmol), HOBt · H_2O (0.05 g, 0.36 mmol), and EDC (0.069 g, 0.36 mmol) in anhydrous CH_3CN (10 mL) at RT. After 17 h, the reaction mixture was concentrated, diluted with CH_2Cl_2 (80 mL), and washed sequentially with 5% $NaHCO_3$ (2 x 20 mL) and brine (20 mL). Drying ($MgSO_4$), concentration, and silica gel chromatography (7% MeOH/CH_2Cl_2) gave the title compound (0.05 g, 36%) as a white solid: MS (ES) m/e 552.2 $(M+H)^+$.

b) (S)-2,3,4,5-Tetrahydro-7-[[bis[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

1.0 N LiOH (0.23 mL, 0.23 mmol) was added dropwise at RT to a mixture of methyl (S)-2,3,4,5-tetrahydro-7-[[bis[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.05 g, 0.09 mmol) in THF (6 mL) and H_2O (4 mL). After 1 h, the reaction mixture was concentrated to a small volume on the rotavap and cooled in an ice bath before neutralizing with 1.0 N AcOH (0.3 mL). The solid was collected, washed with cold H_2O, and air dried to give the title compound (0.048 g, 98%) as a white solid: MS (ES) m/e 538.2 $(M+H)^+$.

Example 33

Preparation of (±)-2,3,4,5-tetrahydro-7-[[bis[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenethyl)-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (±)-2,3,4,5-tetrahydro-7-[[bis[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenethyl)-1H-1,4-benzodiazepine-2-acetate

Diisopropylethylamine (0.3 mL, 1.74 mmol) was added to a stirred solution of methyl (±)-7-carboxy-3-oxo-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (0.11 g, 0.29 mmol), bis[(benzimidazol-2-yl)methyl]amine tris(trifluoroacetate) (0.18 g, 0.29 mmol), HOBt · H_2O (0.058 g, 0.43 mmol), and EDC (0.083 g, 0.43 mmol) in anhydrous CH_3CN (12 mL) at RT. After 21 h, the reaction mixture was concentrated, diluted with CH_2Cl_2 (100 mL), and washed sequentially with 5% $NaHCO_3$ (2 x 20 mL) and brine (20 mL). Drying ($MgSO_4$), concentration, and silica gel chromatography (7% MeOH/CH_2Cl_2) gave the title compound (0.13 g, 70%) as a white solid: MS (ES) m/e 642.2 $(M+H)^+$.

b) (±)-2,3,4,5-Tetrahydro-7-[[bis[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenethyl)-1H-1,4-benzodiazepine-2-acetic

1.0 N LiOH (0.6 mL, 0.6 mmol) was added dropwise at RT to a mixture of methyl (±)-2,3,4,5-tetrahydro-7-[[bis[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenethyl)-1H-1,4-benzodiazepine-2-acetate (0.13 g, 0.20 mmol) in THF (5 mL) and H_2O (5 mL). After 18 h, the reaction mixture was concentrated to a small volume on the rotavap and cooled in an ice bath before neutralizing with 1.0 N AcOH (0.6 mL). The solution was lyophilized to a crude product (0.092 g, 77%) as

a white powder. ODS chromatography (step gradient, 5%-30% CH_3CN/H_2O containing 0.1% TFA) afforded the title compound as a white powder: MS (ES) m/e 628.2 $(M+H)^+$.

Example 34

Preparation of ethyl (±)-3-[[[2-(benzimidazol-2-yl)ethyl]amino]succinoyl]amino-4-pentynoate

a) (±)-4-Ethynyl-2-azetidinone

4-Acetoxy-2-azetidinone (9.0 g, 69.7 mmol) was added slowly to a solution of ethynylmagnesiumchloride (31 mL of a 0.5 M THF solution, 0.55 mmol) at 0°C. After 1.5 h, 1.0 N HCl (100 mL) was added, and the mixture was taken up in EtOAc (300 mL) and washed sequentially with 1.0 N HCl (100 mL), saturated $NaHCO_3$ (100 mL), and brine (100 mL). After drying ($MgSO_4$) and concentration, the title compound (4.57 g, 69%) was obtained as a light brownish solid: MS (ES) m/e 96.0 $(M+H)^+$.

b) Ethyl (±)-3-amino-4-pentynoate

A mixture of (±)-4-ethynyl-2-azetidinone (1.3 g, 13.68 mmol), EtOH (54 mL), and concentrated HCl (6 mL) was heated to reflux for 18 h. The reaction was cooled to RT before adjusting the pH to 8.0 using saturated $NaHCO_3$. The reaction was extracted with EtOAc (3 x 70 mL), and the combined EtOAc layers were washed with brine (50 mL). Drying ($MgSO_4$) and concentration gave the title compound (1.06 g, 55%) as a brownish liquid: MS (ES) m/e 141.9 $(M+H)^+$.

c) Methyl-[[2-(benzimidazol-2-yl)ethyl]amino]succinate

3-Carbomethoxypropionylchloride(0.6 g, 4.0 mmol) was added at 0°C to a stirred solution of 2-aminoethylbenzimidazole diacetate (1.13 g, 4.0 mmol) and diisopropylethylamine (2.59 g, 20 mmol) in dry CH_2Cl_2 (45 mL). After stirring for 1.5 h at RT, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed sequentially with H_2O (30 mL), 5% $NaHCO_3$ (30 mL), and brine (30 mL). Drying ($MgSO_4$), concentration, and silica gel chromatography (8% $MeOH/CH_2Cl_2$) gave the title compound (0.2 g, 18%) as a yellow solid: MS (ES) m/e 276.4 $(M+H)^+$.

d) [[2-(Benzimidazol-2-yl)ethyl]amino]succinic acid

A mixture of methyl-[[2-(benzimidazol-2-yl)ethyl]amino]succinate(0.2 g, 0.73 mmol), 1.0 N NaOH (1.82 mL, 1.82 mmol) and MeOH (10 mL) was stirred at RT for 24 h, then was concentrated to dryness. H_2O (5 mL) was added, the solution was neutralized with 1.0 N HCl (1.82 mL), and the resulting solution was lyophilized to give the crude title compound (0.23 g) as an off-white powder: MS (ES) m/e 261.9 $(M+H)^+$.

e) Ethyl (±)-3-[[[2-(benzimidazol-2-yl)ethyl]amino]succinoyl]amino-4-pentynoate

Diisopropylethylamine (0.32 mL, 1.83 mmol) was added to a stirred solution of ethyl (±)-3-amino-4-pentynoate (0.12 g, 0.88 mmol), [[2-(benzimidazol-2-yl)ethyl]amino]succinic acid (0.19 g, 0.73 mmol), HOBt · H_2O (0.15 g, 1.1 mmol), and EDC (0.21 g, 1.1 mmol) in anhydrous CH_3CN (15 mL) and DMF (3 mL) at RT. After 23 h, the reaction mixture was concentrated, diluted with CH_2Cl_2 (100 mL), and washed sequentially with 5% $NaHCO_3$ (2 x 25 mL) and brine (25 mL). Drying ($MgSO_4$), concentration, and silica gel chromatography (7% MeOH/CH_2Cl_2) gave the title compound (0.07 g, 25%) as a white solid: MS (ES) m/e 385.4 $(M+H)^+$.

Example 35

Preparation of (±)-3-[[[2-(Benzimidazol-2-yl)ethyl]amino]succinoyl]amino-4-pentynoic acid

a) (±)-3-[[[2-(Benzimidazol-2-yl)ethyl]amino]succinoyl]amino-4-pentynoic acid

1.0 N LiOH (0.78 mL, 0.78 mmol) was added dropwise at RT to a mixture of ethyl (±)-3-[[[2-(benzimidazol-2-yl)ethyl]amino]succinoyl]amino-4-pentynoate (0.12 g, 0.31 mmol) in THF (5 mL), H_2O (5 mL) and CH_3CN (1 mL). After 3 h, the reaction mixture was concentrated to a small volume on the rotavap and cooled in an ice bath before neutralizing with 1.0 N AcOH (0.78 mL). The solution was lyophilized to a crude product (0.167 g) as a white powder. ODS chromatography (10% CH_3CN/H_2O containing 0.1% TFA) afforded the title compound as a white powder: MS (ES) m/e 357.1 $(M+H)^+$.

Example 36

Preparation of (±)-3-[[[4-(4-Azabenzimidazol-2-yl)butanoyl]glycyl]amino]-4-pentynoic acid (SB-237554)

a) Methyl (4-azabenzimidazol-2-yl)butyrate

Triethylamine (319 mL, 22.9 mmol) was added to a mixture of 2,3-diaminopyridine (2.5 g, 22.9 mmol) and methyl 4-(chloroformyl)butyrate (3.77g, 22.9 mmol) in dry THF (50 mL) at 0°C. After stirring for 16 h at RT, the reaction was concentrated to dryness under vacuum. The residue was dissolved in glacial AcOH (25 mL) and was heated at 110°C. After 93 h, the reaction was allowed to cool to RT and was concentrated under vacuum. The dark brown residue was diluted with H_2O (40 mL) and CH_2Cl_2 (40 mL), and the mixture was neutralized to pH 7 using 5 N NaOH. The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (2x100 mL). The combined organic layers were washed sequentially with 5% $NaHCO_3$ (2 x 30 mL)and brine (30 mL). Drying ($MgSO_4$), concentration, and silica gel chromatography (7% MeOH/CH_2Cl_2) gave the title compound (0.47, 9%): MS (ES) m/e 220.0 $(M+H)^+$.

b) (4-Azabenzimidazol-2-yl)butyric acid

A mixture of methyl (4-azabenzimidazol-2-yl)butyrate (0.47 g, 2.13 mmol), 1.0 N NaOH (6 mL, 6.0 mmol) and MeOH (10 mL) was stirred at RT for 5.5 h, then was concentrated to dryness. The residue was diluted with H_2O (2 mL) and neutralized with 1.0 N HCl (0.73 mL). The resulting solid was collected and air dried to give the title compound (0.32 g, 73%) as a yellow powder: MS (ES) m/e 206.0 $(M+H)^+$.

c) Ethyl (±)-3-[[(N-tert-butoxycarbonyl)glycyl]amino]-4-pentanoate

Diisopropylethylamine (0.92 mL, 5.32 mmol) was added to a stirred solution of ethyl (±)-3-amino-4-pentynoate (0.3 g, 2.13 mmol), Boc-Gly (0.56 g, 3.19 mmol), HOBt · H_2O (0.43 g, 3.19 mmol), and EDC (0.61 g, 3.19 mmol) in anhydrous CH_3CN (15 mL) at RT. After 34 h, the reaction mixture was concentrated, diluted with CH_2Cl_2 (70 mL), and washed sequentially with 5% $NaHCO_3$ (2x15 mL) and brine (15 mL). Drying ($MgSO_4$), concentration, and silica gel chromatography (1:1 EtOAc/Hexane) gave the title compound (0.5 g, 79%) as a colorless oil: MS (ES) m/e 299.2 $(M+H)^+$.

d) Ethyl (±)-3-[(glycyl)amino]-4-pentanoate trifluoroacetate

A solution of TFA (5 mL) and CH_2Cl_2 (15 mL) at RT was added all at once to ethyl (±)-3-[[(N-tert-butoxycarbonyl)glycyl]amino]-4-pentanoate (0.5 g, 1.68 mmol). After 30 min, the solution was concentrated on the rotavap, and the residue

was reconcentrated from toluene (to remove residual TFA) to afford the title compound (0.55g, 106%) as a light yellow syrup: MS (ES) m/e 199.2 $(M+H)^+$.

e) Ethyl (±)-3-[[[4-(4-azabenzimidazol-2-yl)butanoyl]glycyl]amino]-4-pentynoate

Diisopropylethylamine (0.94 mL, 5.43 mmol) was added to a stirred solution of ethyl (±)-3-[(glycyl)amino]-4-pentanoate trifluoroacetate (0.55 g, 1.76 mmol), (4-azabenzimidazol-2-yl)butyric acid (0.32 g, 1.55 mmol), HOBt · H_2O (0.31 g, 2.33 mmol), and EDC (0.45 g, 2.33 mmol) in anhydrous CH_3CN (15 mL) at RT. After 64 h, the reaction mixture was concentrated, diluted with CH_2Cl_2 (100 mL), and washed sequentially with 5% $NaHCO_3$ (2 x 25 mL) and brine (25 mL). Drying ($MgSO_4$), concentration, and silica gel chromatography (7% MeOH/CH_2Cl_2) gave the title compound (0.11 g, 18%) as a white solid: MS (ES) m/e 386.4 $(M+H)^+$.

f) (±)-3-[[[4-(4-Azabenzimidazol-2-yl)butanoyl]glycyl]amino]-4-pentynoic acid

1.0 N LiOH (0.71 mL, 0.71 mmol) was added dropwise at RT to a mixture of ethyl (±)-3-[[[4-(4-azabenzimidazol-2-yl)butanoyl]glycyl]amino]-4-pentynoate (0.11 g, 0.285 mmol) in THF (5 mL), H_2O (5 mL) and CH_3CN (1 mL). After 2 h, the reaction mixture was concentrated to a small volume on the rotavap and cooled in an ice bath before neutralizing with 1.0 N AcOH (0.70 mL). The solution was lyophilized to a crude product (0.1 g, 100%) as a white powder. ODS chromatography (5% CH_3CN/H_2O containing 0.1% TFA) afforded the title compound as a white powder MS (ES) m/e 358.4 $(M+H)^+$.

Example 37

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) Dimethyl D-malate-O-trifluoromethanesulfonate

A solution of dimethyl-D-malate (12.96 g, 80 mmol) and pyridine (6.8 mL, 84 mmol) in CH_2Cl_2 dry (50 mL) was added dropwise under argon at 0°C to a solution of trifluoromethanesulfonic anhydride (14.2 mL, 84 mmol) in dry CH_2Cl_2 (40 mL) in a flame dried flask. The resulting yellowish-orange mixture was stirred at 0°C for 30 min, and then at RT for 4 hr. The reaction was quenched by adding H_2O (50 mL), and the layers were separated. The organic layer was washed sequentially with H_2O (3 x) and brine. Drying ($MgSO_4$) and concentration gave the title compound (22.45 g, 95%) as an off white solid: MS(ES) m/e 295 $(M + H)^+$.

b) Dimethyl-N-(2-cyanophenyl)-D-aspartate

A solution of dimethyl D-malate-O-trifluoromethanesulfonate (22.4 g, 76.2 mmol) in $CHCl_3$ (40 mL) and hexanes (40 mL) was added at to a solution of 2-aminobenzonitrile (9.0 g, 76.2 mmol) and 2,6-di-tert-butylpyridine in $CHCl_3$ (50 mL) and hexanes (50 mL) in a flame dried flask at 0°C under argon. The resulting mixture was stirred at 0°C for 30 min, then at RT for 3 days. The solvent was removed in vacuo and the residue was taken into EtOAc and washed sequentially with 5% HCl (10 x) and brine. Drying ($MgSO_4$), concentration and silica gel flash chromatography (12% EtOAc/hexanes) gave the title compound (12.3 g, 62%) as a clear oil: MS(ES) m/e 263.3 $(M + H)^+$.

c) Methyl (S)-2,3,4,5-tetrahydro-3-oxo-1H-1,4-benzodiazepine-2-acetate

A mixture of dimethyl-N-(2-cyanophenyl)-D-aspartate (12 g, 45.7 mmol), Et_3N (7.64 mL, 54.84 mmol) and Raney-Ni (46 g, wet, prewashed with CH_3OH) in CH_3OH (200 mL) was stirred at RT under H_2 (balloon) for 2 days. The catalyst was removed by filtration and washed with CH_3OH (3 x). Concentration and silica gel flash chromatography (0-5% CH_3OH/CH_2Cl_2) gave the title compound (7.93 g, 74 %) as a white solid: MS(ES) m/e 235.3 $(M + H)^+$.

d) Methyl (S)-2,3,4,5-tetrahydro-7-bromo-3-oxo-1H-1,4-benzodiazepine-2-acetate

Tetrabutylammonium tribromide (5.16 g, 10.7 mmol) was added portionwise to a solution of methyl (S)-2,3,4,5-tetrahydro-3-oxo-1H-1,4-benzodiazepine-2-acetate (2.5 g, 10.7 mmol) in $CHCl_3$ (50 mL), and the mixture was stirred at RT for 2 days. H_2O (30 mL) was then added, and the organic layer was separated and washed sequentially with H_2O and brine. Drying ($MgSO_4$), concentration, and silica gel flash chromatography (0-5% CH_3OH/CH_2Cl_2) gave the title compound (1.99 g, 60%)) as a white solid: MS(ES) m/e 313.0 $(M + H)^+$.

e) Methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate

A mixture containing methyl (S)-2,3,4,5-tetrahydro-7-bromo-3-oxo-1H-1,4-benzodiazepine-2-acetate (624 mg, 2 mmol), 2-(aminomethyl)-4-aza-5-methylbenzimidazole dihydrochloride (695 mg, 2.8 mmol), DIEA (1.8 mL, 10 mmol), and $(Ph_3P)_2PdCl_2$ (126 mg, 0.18 mmol) in NMP (22 mL) was heated to 110°C under a CO balloon for 48 hr. The solvent was removed on the rotavap (high vacuum) and the residue was purified by silica gel flash chromatography (0.5 - 5%

CH_3OH/CH_2Cl_2) to give the title compound (170 mg, 19.5%) as a pale yellow solid: MS (ES) m/e 437.5 $(M + H)^+$.

f) (S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

1.0 M LiOH (0.6 mL, 0.6 mmol) was added dropwise to a solution of methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate (170 mg, 0.39 mmol) in CH_3OH (5 mL) and THF (5 mL)at RT. The resulting mixture was stirred for 20 hr and then was concentrated. The residue was dissolved in H_2O, acidified with 30% TFA, and purified by ODS chromatography (5% CH_3CN/H_2O containing 0.1% TFA). Concentration and lyophilization gave the title compound as an off white powder: $[\alpha]_n^{25}$ -74.5° (c = 1, CH_3OH); MS (ES) m/e 423.2 $(M + H)^+$. Anal. Calcd for $C_{21}H_{22}N_6O_4 \cdot 2$ TFA $\cdot$ 1.75 H_2O: C, 44.03; H, 4.06; N, 12.32. Found: C, 44.33; H, 4.04; N, 12.28.

Example 38

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (S)-2,3,4,5-tetrahydro-7-iodo-3-oxo-1H-1,4-benzodiazepine-2-acetate

Pyridine-ICl complex: Iodine monochloride (100 mL, 1 M solution in CH_2Cl_2) was added slowly to a solution of pyridine (8.5 mL, 105 mmol) in dry CH_2Cl_2 (20 mL) at 5°C under argon so that the temperature was maintained between 10 - 15°C. The mixture was stirred at 5 - 10°C for 20 min, then hexanes (50 mL) was added, and the mixture was stirred in the cold bath for another 30 min. The solid was collected by suction filtration, washed sequentially with hexanes and petroleum ether, and dried to afford the reagent (22.5 g) as a yellow, crystalline solid.

Pyridine-ICl complex (1.27 g, 5.28 mmol) was added portionwise to a solution of methyl (S)-2,3,4,5-tetrahydro-3-oxo-1H-1,4-benzodiazepine-2-acetate (1.18 g, 4.8 mmol) in CH_2Cl_2 (20 mL) and CH_3OH (20 mL). The resulting mixture was stirred at RT for 40 min, then 1 M $NaHSO_3$ (20 mL) was added. The solid was collected by suction filtration and washed with Et_2O. Drying yielded the title compound (1.72 g, quantitative) as an off-white solid: MS (ES) m/e 361.2 $(M + H)^+$.

b) Methyl (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate

A mixture of methyl (S)-2,3,4,5-tetrahydro-7-iodo-3-oxo-1H-1,4-benzodiazepine-2-acetate (1.08 g, 3 mmol), 2-aminomethylbenzimidazole dihydrochloride hydrate (924 mg, 4.2 mmol), DIEA (2.6 mL, 15 mmol), and $(Ph_3P)_2PdCl_2$ (211 mg, 0.3 mmol) in NMP (30 mL) was heated to 110°C under a CO balloon for 3 hr. The solvent was removed on the rotavap (high vacuum) and the residue was purified by silica gel flash chromatography (0-7% CH_3OH/CH_2Cl_2) to afford the title compound (530 mg, 44%) as an off white solid: MS(ES) m/e 408.1 $(M + H)^+$.

c) (S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure of Example 37(f), except substituting methyl (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate for methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate, the title compound (66%) was prepared as a white powder: $[\alpha]_D^{25}$ -145.3° (c = 1, CH_3OH); MS (ES) m/e 394.2 $(M + H)^+$. Anal. Calcd for $C_{20}H_{19}N_5O_4 \cdot 2\ TFA \cdot 0.125\ H_2O$: C, 46.22; H, 3.43; N, 11.23. Found: C, 46.13; H, 3.78; N, 11.49.

Example 39

Preparation of (±)-N-[2-(aminomethyl)-4-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]aspartic acid

a) Methyl (±)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate

EDC (130 mg, 0.75 mmol) was added to a solution of methyl (±)-2,3,4,5-tetrahydro-7-carboxy-3-oxo-1H-1,4-benzodiazepine-2-acetate (190 mg, 0.68 mmol), 2-(aminomethyl)-4-aza-5-methylbenzimidazole dihydrochloride (169 mg, 0.68 mmol), HOBt · H_2O (101 mg, 0. 75 mmol), and DIEA (0.39 mL. 2.24 mmol) in anhydrous DMF at RT. After 20 hr, the reaction was concentrated on the rotavap (high vacuum), and the residue was chromatographed on silica gel (1 - 6.5% CH_3OH/CH_2Cl_2) to afford the title compound (260 mg, 88%) as a white solid: MS (ES) m/e 437.5 $(M + H)^+$.

b) (±)-N-[2-(Aminomethyl)-4-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]aspartic acid

Following the procedure of Example 37(f), except substituting methyl (±)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate for methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate, the title compound (66%) was prepared as a white powder: MS (ES) m/e 441.2 $(M + H)^+$. Anal. Calcd for $C_{21}H_{24}N_6O_5 \cdot 2$ TFA $\cdot 2.25$ H_2O: C, 42.08; H, 4.38; N, 11.78. Found: C, 42.01; H, 4.18; N, 11.55.

Example 40

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate

Following the procedure of Example 38(b), except substituting 2-(aminomethyl)-4-aza-5-methylbenzimidazole dihydrochloride for 2-aminomethylbenzimidazole dihydrochloride hydrate, the title compound (63%) was prepared as an amber solid: MS (ES) m/e 423 $(M + H)^+$.

b) (S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure of Example 37(f), except substituting methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate for methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate, the title compound (50%) was prepared as a white powder: MS (ES) m/e 409.2 $(M + H)^+$. Anal. Calcd for $C_{20}H_{20}N_6O_4 \cdot 1.75$ TFA $\cdot$ H_2O: C, 45.09; H, 3.82; N,3 .45. Found: C, 45.18; H, 4.10; N, 13.58.

Example 41

Preparation of (S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-[2-(pyrid-3-yl)ethyl]-1H-1,4-benzodiazepine-2-acetate

a) tert-Butyl 4-fluoro-3-[[2-(pyrid-3-yl)ethyl]amino]benzoate

A mixture of tert-butyl 4-fluoro-3-methylbenzoate (3.83 g, 18.22 mmole), NBS (3.57 g, 20.24 mmole), benzoyl peroxide (0.22 g, 0.91 mmole), and CCl_4 (90 mL) was heated at reflux. After 16 hr, the reaction was cooled in ice/H_2O and filtered, and the filtrate was concentrated. The residue was passed through a short pad of silica gel (20 % EtOAc/hexane) to remove baseline materials, and the filtrate was concentrated. The residue was dissolved in THF (90 mL), and 3-(2-aminoethyl)pyridine (6.97 g, 57 mmol).) was added rapidly. The addition appeared to be mildly endothermic. The reaction was stirred overnight then was concentrated. The residue was diluted with Et_2O (100 mL) and washed sequentially with 1.0 N NaOH (30 mL), H_2O (30 mL), and brine (30 mL). Drying ($MgSO_4$), concentration, and silica gel chromatography (10 % MeOH/CH_2Cl_2) gave the title compound (2.58 g, 59 %) as a yellow oil: MS (ES) m/e 331 $(M + H)^+$.

b) tert-Butyl (S)-4-fluoro-3-[2-aza-4-(benzyloxycarbonyl)amino-3,6-dioxo-6-methoxy-2-[2-(pyrid-3-yl)ethyl]hexyl]benzoate

DCC (1.86 g, 9 mmol)was added to a solution of tert-butyl 4-fluoro-3-[[2-(pyrid-3-yl)ethyl]amino]benzoate (2.7 g,.8.18 mmol), N-Cbz-L-aspartic acid β-methyl ester (*J. Am. Chem. Soc.* **1957**, *79*, 5697; 2.53 g, 9 mmol.), and HOBt · H_2O (1.2 g, 9 mmol) in anhydrous DMF (10 mL) at RT. After 24 hr, the mixture was diluted with Et_2O (25 mL) and filtered. The filtrate was concentrated to dryness, and the residue was diluted with Et_2O (50 mL) and washed with H_2O (2 x 10 mL) and brine (10 mL). Drying ($MgSO_4$), concentration, and silica gel chromatography (CH_2Cl_2) gave the title compound (2.4 g, 49%)as a colorless oil: MS (ES) m/e 594 $(M + H)^+$.

c) tert-Butyl (S)-4-fluoro-3-[4-amino-2-aza-3,6-dioxo-6-methoxy-2-[2-(pyrid-3-yl)ethyl]hexyl]benzoate

A mixture of tert-butyl (S)-4-fluoro-3-[2-aza-4-(benzyloxycarbonyl)amino-3,6-dioxo-6-methoxy-2-[2-(pyrid-3-yl)ethyl]hexyl]benzoate (2.4 g, 4 mmol.), 10 % Pd/C (184 mg, 0.17 mmole), and MeOH (17 mL) was shaken at RT under H_2 (50 psi). After 1.5 hr, the reaction was filtered through celite® and concentrated. Silica

gel chromatography (10 % MeOH in 1:1 EtOAc/$CHCl_3$) gave the title compound (1.1 g, 59 %) as a colorless oil: MS (ES) 460 $(M + H)^+$.

d) Methyl (S)-2,3,4,5-tetrahydro-7-(tert-butoxycarbonyl)-4-[2-(pyrid-3-yl)ethyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate

A solution of tert-butyl (S)-4-fluoro-3-[4-amino-2-aza-3,6-dioxo-6-methoxy-2-[2-(pyrid-3-yl)ethyl]hexyl]benzoate (0.64 g 1.39 mmol) in anhydrous DMSO (5.7 mL) was heated under argon in an oil bath set at 120-125°C. After 17.5 hr, the reaction was cooled in ice/H_2O and diluted with H_2O (12 mL). The mixture was extracted with EtOAc (3 x 20 mL), and the combined EtOAc layers were washed with H_2O (10 mL) and brine (10 mL). Drying ($MgSO_4$), concentration, and silica gel chromatography (9:1 CH_2Cl_2/MeOH) gave the title compound (0.15 g, 33%) as a nearly colorless solid: MS (ES) m/e 440 $(M +H)^+$.

e) Methyl (S)-2,3,4,5-tetrahydro-7-carboxy-4-[2-(pyrid-3-yl)ethyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate

4 M HCl/dioxane (0.5 mL) was added to a solution of methyl (S)-2,3,4,5-tetrahydro-7-(tert-butoxycarbonyl)-4-[2-(pyrid-3-yl)ethyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate(0.18 g, 4.1 mmol) in anhydrous CH_2Cl_2 (5 mL) and the reaction was stirred at RT overnight. Concentration in vacuo followed by reconcentration from toluene (3 x 10 mL) gave the title compound (0.12 g, 65%): MS (ES) m/e 384 $(M + H)^+$.

f) Methyl (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-[2-(pyrid-3-yl)ethyl]-1H-1,4-benzodiazepine-2-acetate

A mixture of methyl (S)-2,3,4,5-tetrahydro-7-carboxy-4-[2-(pyrid-3-yl)ethyl]-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.12 g, 0.26 mmol) and thionyl chloride (15 mL) was refluxed for 1 h. The resulting orange solution was concentrated to dryness to leave a yellow-orange foam. This was dissolved in CH_2Cl_2 (10 mL) and added dropwise to a solution containing 2-aminomethylbenzimidazole dihydrochloride hydrate (0.058 g, 0.26 mmol), pyridine (0.72 g, 9.1 mmol), and triethylamine (0.55 g, 5.46 mmol) in CH_2Cl_2 (15 mL) at 0°C under argon. The reaction mixture was then stirred in RT under argon. After 25.5 h, CH_2Cl_2 (200 mL) and 5% $NaHCO_3$ (50 mL) were added to the reaction mixture to give a light yellow precipitate which was filtered and air-dried to give the title compound (0.030g.,22% yield): MS (ES) m/e 513 $(M+H)^+$.

g) (S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-[2-(pyrid-3-yl)ethyl]-1H-1,4-benzodiazepine-2-acetate

1.0 N LiOH (0.57 mL, 0.57 mmol) was added dropwise at RT to a mixture of methyl (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-[2-(pyrid-3-yl)ethyl]-1H-1,4-benzodiazepine-2-acetate (0.030 g, 0.059 mmol) in THF (4 mL) and H_2O (5 mL). The resulting light brownish-yellow solution was stirred for 21.5 h, then was concentrated on the rotavap. The resulting residue was lyophilized to give the crude product as a yellowish powder. Preparative HPLC (PRP-1® column, step gradient, 10-20% CH_3CN/H_2O containing 0.1% TFA) afforded the title compound (0.010g 34% yield): MS (ES) m/e 499$(M+H)^+$. Anal. Calcd .for $C_{27}H_{26}N_6O_4 \cdot 3\ C_2HF_3O2 \cdot 3\ HCl \cdot 3\ H_2O$: C, 37.41; H, 3.41; N,7.52. Found: C, 37.6; H, 3.52; N, 7.52.

Example 42

Preparation of Ethyl (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

a) Ethyl (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

HCl gas was bubbled into EtOH (200 mL) for 10 min, then (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid (2.00 g, 4.5 mmol) was added. The reaction was stirred at RT for 24 hr, then was concentrated to dryness on the rotavap. The residue was reconcentrated from toluene (2 x) to remove residual EtOH, then was chromatographed on silica gel (gradient: 7% $MeOH/CH_2Cl_2$ (1 L) then 10% $MeOH/CH_2Cl_2$). The resulting residue was dissolved in EtOH, and Et_2O was added to precipitate a solid. This was collected and washed with Et_2O to afford the title compound as a white solid: MS (ES) m/e 450.2 $(M + H)^+$. Anal. Calcd for $C_{24}H_{27}N_5O_4 \cdot 1.5\ H_2O$: C, 60.49; H, 6.35; N, 14.70. Found: C, 60.41; H, 6.27; N, 14.38.

Example 43

Preparation of 4-[[[3-(1H-benzimidazol-2-yl)propyl]amino]carbonyl]piperidine-1-acetic acid

a) 2-[3-(N-tert-Butoxycarbonyl)aminopropyl]benzimidazole

A solution of isobutylchloroformate (10.2 mL, 79 mmol) in THF (25 mL) was added to a solution of 4-(tert-butoxycarbonyl)aminobutyric acid (*Organic Synthesis* **1984**, *63*, 160; 13.5 g, 0.066 mole) and triethylamine (11 mL, 80 mmol) in THF (50 mL) at 0°C under argon. After 0.5 h, a solution of 1,2-phenylenediamine (7 g, 64.8 mmole) in THF (50 mL) was added dropwise to the resulting white suspension. The reaction was stirred for 18 h, then was filtered, and the filtrate was concentrated to give a semi-solid. This was dissolved in AcOH (100 mL), and the solution was heated at 70°C for 18 h. The reaction mixture was concentrated, and the residue was reconcentrated several times from toluene. Silica gel flash chromatography gave the title compound (6.0 g, 33%): MS (ES) m/e 276 $[M+H]^+$.

b) 2-(3-Aminopropyl)benzimidazole dihydrochloride

A solution of 2-[3-(N-tert-butoxycarbonyl)aminopropyl]benzimidazole (1.2 g, 4.3 mmol) and 4 M HCl in dioxane (20 mL) in CH_2Cl_2 (25 mL) was stirred at RT for 18 h. The resulting white suspension was filtered to give the title compound (1.07 g, 97%).

c) Ethyl 4-[[[3-(1H-benzimidazol-2-yl)propyl]amino]carbonyl]piperidine-1-acetate

A mixture of ethyl 4-carboxypiperidine-1-acetate hydrochloride (Yellin's SB 223913 CIP)(0.76 g, 3 mmol) in thionyl chloride (10 mL) was heated to reflux for 15 min, then was concentrated to dryness. After evaporation several times from toluene, the residue was dissolved with 2-(3-aminopropyl)benzimidazole dihydrochloride (0.77 g, 3 mmol) and DIEA (3 mL) in DMF (25 mL). After 18 h, the reaction mixture was partitioned between EtOAc (50 mL) and 5% $NaHCO_3$ (100 mL), and extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed sequentially with H_2O and saturated NaCl solution, then were dried over $MgSO_4$. Concentration and silica gel flash chromatography (6% MeOH/CH_2Cl_2) gave the title compound (40 mg, 3%).

b) 4-[[[3-(Benzimidazol-2-yl)propyl]amino]carbonyl]piperidine-1-acetic acid

1N NaOH solution (0.4 mL, 0.4 mmol) was added to a stirred solution of ethyl 4-[[3-(1H-benzimidazol-2-yl)propylamino]carbonyl]piperidine-1-acetate (40 mg, 0.1 mmol) in MeOH (10 mL)at RT. After 18 h, the mixture was neutralized with AcOH (1 mL) and concentrated to remove the MeOH. The aqueous solution was loaded onto an XAD-2 column, and eluted with H_2O (500 mL), then with 20%

CH_3CN/ H_2O. The fractions containing the product were pooled and lyophilized to give the title compound (9 mg, 25%). MS (ES) m/e 345.2 $[M+H]^+$. Anal. Calcd for $C_{18}H_{24}N_4O_3 \cdot 0.75\ H_2O$: C, 60.40; H, 7.18; N, 15.65. Found: C, 60.48; H, 7.16; N, 15.40.

Example 44

Preparation of 4-[[[3-(benzimidazol-2-yl)propyl]amino]carbonyl]phenylacetic acid

a) Ethyl 4-[[[3-(benzimidazol-2-yl)propyl]amino]carbonyl]-1-phenylacetate

A mixture of ethyl 2-(4-carboxyphenyl)acetate (Yellin's SB 223913 CIP)(0.5 g, 2.4 mmol), 2-(3-aminopropyl)benzimidazole dihydrochloride (0.7 g, 2.8 mmol), HOBt · H_2O (0.36 g, 2.6 mmol), EDC (0.5 g, 2.6 mmol), and DIEA (1.5 mL, 8.8 mmol) in DMF (15 mL) was warmed briefly and stirred at RT for 18 h. The reaction mixture was partitioned between EtOAc (50 mL) and 5% $NaHCO_3$ (100 mL), and extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed sequentially with H_2O and saturated NaCl solution, then were dried over $MgSO_4$. The evaporated residual solid was triturated with Et_2O to give the title compound (0.56 g, 66%): MS (ES) m/e 366.0$[M+H]^+$. Anal. Calcd for $C_{21}H_{23}N_3O_3 \cdot 0.25\ H_2O$: C, 68.18; H,6.40; N, 11.36. Found: C, 68.16; H,6.26; N,11.36.

b) 4-[[[3-(Benzimidazol-2-yl)propyl]amino]carbonyl]phenylacetic acid

1 N NaOH solution (6 mL, 6 mmol) was added to a stirred solution of ethyl 4-[[[3-(1H-benzimidazo-2-yl)propyl]amino]carbonyl]-1-phenylacetate (0.38 g, 1 mmol) in MeOH (15 mL)at RT. After 4 h, the mixture was neutralized with AcOH (6 mL) and the resulting solid was filtered to give the title compound (77 mg, 22%): MP 108-110°C; MS (ES) m/e 345.2 $[M+H]^+$. Anal. Calcd for $C_{19}H_{19}N_3O_3 \cdot 0.6\ H_2O$: C, 65.54; H, 5.85; N, 12.07. Found: C, 65.63; H, 5.65; N, 11.95.

Example 45

Preparation of (S)-2,3,4,5-tetrahydro-4-methyl-3-oxo-7-[[[(5-trifluoromethylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid

a) 3,4-Diaminobenzotrifluoride

4-Amino-3-nitrobenzotrifluoride (3.7070 g, 17.98 mmol) was dissolved in MeOH, and a catalytic amount of 10% Pd/C was added. The reaction was purged with H_2, and stirred at RT under H_2 (balloon). After 24 hr, the reaction was filtered through a bed of celite®, and the filtrate was evaporated under vacuum to yield the title compound (3.0878 g, 98%). The material was used without characterization.

b) 2-[N-(Benzyloxycarbonyl)-N-methyl]aminomethyl-5-trifluoromethylbenzimidazole

Cbz-sarcosine (3.9950 g, 17.13 mmol) was dissolved in dry THF, and isobutylchloroformate (2.5 mL, 19.27 mmol) was added, followed by triethylamine (5.0 mL, 35.95 mmol). The mixed anhydride was allowed to form at RT for 30 min, then was added to a solution of 3,4-diaminobenzotrifluoride (3.0818 g, 7.53 mmol) in dry THF. After 20 hours at RT, the reaction was evaporated under vacuum. The residue was partitioned between EtOAc and 1.0 N $NaHCO_3$, and the layers were separated. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried ($MgSO_4$), filtered and evaporated under vacuum. The residue was reconcentrated from toluene, then was dissolved in glacial AcOH (125 mL). The solution was heated at 110°C for 24 hr, then the AcOH was evaporated under vacuum. The residue was reconcentrated from toluene, then was adsorbed onto silica gel and loaded onto a dry silica gel flash chromatography column. The column was eluted with 1:1 $CHCl_3/Et_2O$ to afford the title compound (2.9397 g, 47.2%): TLC R_f (1:1 CH_2Cl_2/Et_2O) 0.57; MS (ES) m/e 364.2 $(M+H)^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 8.0 - 7.2 (m, 9H), 5.05 (s, 2H), 4.84 (s, 2H), 3.07 (s, 3H).

c) 2-(Methylaminomethyl)-5-trifluoromethylbenzimidazole

2-[N-(Benzyloxycarbonyl)-N-methyl]aminomethyl-5-trifluoromethylbenzimidazole (2.9397 g, 8.09 mmol) was dissolved in MeOH, and a catalytic amount of 10% Pd/C was added. The reaction was purged with H_2, then was stirred at RT under H_2. After 5 hr, the reaction mixture was filtered through a bed of celite®, and the filtrate was evaporated under vacuum to leave a tan colored oil. Analysis by 400 MHz NMR showed the Cbz protecting group was still present, so the residue was resubmitted to the reaction conditions. After 18 hr, the catalyst was removed by filtration through a bed of celite® and the filtrate was evaporated under vacuum to yield the title compound (1.7809 g, 96%): ^1H NMR (250 MHz, $CDCl_3$) δ 7.76 - 7.32 (m, 4H), 4.32 (s, 2H), 2.59 (s, 3H).

d) Methyl (S)-2,3,4,5-tetrahydro-4-methyl-3-oxo-7-[[[(5-trifluoromethylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-1,4-benzodiazepine-2-acetate

Methyl (S)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (179.2 mg, 0.61 mmol) was weighed into a 100 mL round bottomed flask. CH_3CN (10 mL) was added, followed by HOBt · H_2O (97.9 mg, 0.72 mmol) and EDC (149.3 mg, 0.78 mmol). After all the solids had dissolved, a solution of 2-(methylaminomethyl)-5-trifluoromethylbenzimidazole (186.1 mg, 0.81 mmol) in CH_3CN was added with diisopropylethylamine (0.25 mL, 1.44 mmol). After 24 hr at RT, the reaction was evaporated under vacuum, and the residue was chromatographed on silica gel (3% MeOH/$CHCl_3$) to afford the title compound (308.1 mg, 100%): TLC R_f (5% MeOH/$CHCl_3$) 0.21; ^1H NMR (250 MHz, $CDCl_3$) δ 7.83-7.16 (m, 7H), 5.37 (d, 1H), 5.05-4.70 (m, 3H), 2.96 (m, 3H), 3.72 (s, 3H), 3.16 (s, 2H), 2.11 (s, 3H); MS (ES) m/e 504.0 $(M+H)^+$.

e) (S)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[(5-trifluoromethylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid

Methyl (S)-2,3,4,5-tetrahydro-4-methyl-3-oxo-7-[[[(5-trifluoromethylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-1,4-benzodiazepine-2-acetate (308.1 mg, 0.61 mmol) was dissolved in MeOH (5 mL). H_2O (5 mL) was added, followed by 1.0 N NaOH (2.0 mL, 2.0 mmol). After 24 hr at RT, the reaction was neutralized with 1.0 N HCl (2.0 mL). The milky white mixture was stirred at RT for 15 min, then was diluted with H_2O, and the precipitate was collected on a sintered glass funnel. The white powder was dried in a vacuum desiccator overnight to yield the title compound (268.0 mg, 90%): MS (ES) m/e 490.2 $(M+H)^+$. Anal. Calcd for $C_{23}H_{22}N_5O_4F_3 \cdot 2.25\ H_2O \cdot 0.25$ HCl: C, 51.24; H, 5.00; N, 12.99. Found: C, 51.44; H, 4.96; N, 12.45.

Example 46

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(4,7-dimethoxybenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) 2-[N-(Benzyloxycarbonyl)-N-methyl]aminomethyl-4,7-dimethoxybenzimidazole

Following the procedure of Example 45(b), except substituting 1,2-diamino-3,6-dimethoxybenzene for the 3,4-diaminobenzotrifluoride, the title compound was

prepared: MS (ES) m/e 356.2 $(M+H)^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 7.34 (s, 5H), 6.54 (d, 2H), 5.18 (s, 2H), 4.65 (s, 2H), 3.95 (s, 3H), 3.86 (s, 3H), 3.03 (s, 3H).

b) 4,7-Dimethoxy-2-(methylaminomethyl)benzimidazole

2-[N-(Benzyloxycarbonyl)-N-methyl]aminomethyl-4,7-dimethoxybenzimidazole (186.5 mg, 0.53 mmol) was dissolved in MeOH, and a catalytic amount of 10% Pd/C was added. The reaction was purged with H_2, then was stirred at RT under H_2 (balloon). After 20 hr, the reaction was filtered through celite®, and the filtrate was evaporated under vacuum to yield the title compound (96.9 mg, 83%): ^1H NMR (250 MHz, $CDCl_3$) δ 6.52 (s, 2H), 3.94-3.86 (m, 6H), 2.36 (s, 3H).

c) Methyl (S)-2,3,4,5-tetrahydro-7-[[[(4,7-dimethoxybenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Methyl (S)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (112.3 mg, 0.38 mmol) was weighed into a 100 mL round bottomed flask. CH_3CN was added, followed by HOBt · H_2O (62.3 mg, 0.46 mmol) and EDC (120.0 mg, 0.63 mmol). When the solids had all dissolved, diisopropylethylamine (0.1 mL, 0.57 mmol) was added, followed by a suspension of 4,7-dimethoxy-2-(methylaminomethyl)benzimidazole (96.8 mg, 0.44 mmol) in CH_3CN containing diisopropylethylamine (0.1 mL, 0.57 mmol). After 2.5 days at RT, the reaction was evaporated under vacuum. The residue was evaporated once with toluene, then was chromatographed on silica gel ($CHCl_3$, then 5% MeOH/$CHCl_3$) to afford the title compound (152.0 mg, 80.0%): TLC R_f (5% MeOH/$CHCl_3$) 0.35; MS (ES) m/e 496.2 $(M+H)^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 7.25 (m, 2H), 6.56 (s, 2H), 5.36 (d, 1H), 3.91 (s, 6H), 3.70 (s, 3H), 3.08 (s, 3H).

d) (S)-2,3,4,5-Tetrahydro-7-[[[(4,7-dimethoxybenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure of Example 45(e), methyl (S)-2,3,4,5-tetrahydro-7-[[[(4,7-dimethoxybenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate was saponified to afford the title compound (110.0 mg, 74%): MS (ES) m/e 482.2 $(M+H)^+$. Anal Calcd for $C_{24}H_{27}N_5O_6 \cdot 0.75\ H_2O$: C, 58.23; H, 5.80; N, 14.15. Found: C, 58.26; H, 5.59; N, 13.90.

Example 47

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(4-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) 1,2-Diamino-3-methylbenzene

Following the procedure of Example 45(a), except substituting 2-methyl-6-nitroaniline (3.0204 g, 19.98 mmol) for the 4-amino-3-nitrobenzotrifluoride, the title compound (2.4815 g) was prepared. This was used without characterization.

b) 2-[N-(Benzyloxycarbonyl)-N-methyl]aminomethyl-4-methylbenzimidazole

Cbz-sarcosine (4.6466 g, 19.92 mmol) was dissolved in dry THF in a 100 mL round-bottomed flask. Triethylamine (3.0 mL, 21.57 mmol) was added, followed by isobutylchloroformate (2.8 mL, 21.59 mmol). The white reaction mixture was stirred at RT for 0.5 hr, then was added to a solution of 1,2-diamino-3-methylbenzene (2.4815 g) in dry THF at -20 to -30°C. After 20 min, the reaction was warmed to RT and stirred there for 16 hr. The reaction was evaporated under vacuum and the residue was partitioned between EtOAc and 1.0 N $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organics were dried ($MgSO_4$), filtered, and evaporated under vacuum. The residue was reconcentrated from toluene and the dried solid was dissolved in glacial AcOH (150 mL). The solution was heated at 110°C for 18 hr, then was concentrated under high vacuum. The residue was reconcentrated from toluene, then was adsorbed onto silica gel and loaded onto a dry silica gel flash chromatography column. The column was eluted with 1:1 CH_2Cl_2/Et_2O to afford the title compound (3.1586 g, 51%): MS (ES) m/e 310.2 $(M+H)^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 7.35-7.01 (m, 10H), 5.00 (s, 2H), 4.72 (s, 2H), 2.99 (s, 3H), 2.55 (s, 3H).

c) 4-Methyl-2-(methylaminomethyl)benzimidazole

Following the procedure of Example 45(c), except substituting 2-[N-(benzyloxycarbonyl)-N-methyl]aminomethyl-4-methylbenzimidazole for the 2-[N-(benzyloxycarbonyl)-N-methyl]aminomethyl-5-trifluoromethylbenzimidazole, the title compound (2.9916 g, quantitative) was prepared: ^1H NMR (250 MHz, $CDCl_3$) δ 7.36-7.01 (m, 4H), 4.01 (s, 2H), 2.52 (s, 3H), 2.41 (s, 3H).

d) Methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Methyl (S)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (188.5 mg, 0.64 mmol) was weighed into a 100 mL round bottomed flask. CH_3CN was added, followed, sequentially, by HOBt · H_2O (103.5 mg, 0.77 mmol), EDC (149.3 mg, 0.78 mmol), and diisopropylethylamine (0.15 mL, 0.86 mmol). After 15 min, a solution of 4-methyl-2-(methylaminomethyl)benzimidazole (273.8 mg, 1.56 mmol) in CH_3CN was added. CH_2Cl_2 (5 mL) was added to dissolve some material. After 18 hr at RT, the reaction was concentrated, and the residue was chromatographed on silica gel (5% MeOH/$CHCl_3$) to afford the title compound (307.3 mg, quantitative): MS (ES) m/e 450.2 $(M+H)^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 7.23-7.03 (m, 7H), 6.41 (br s, 1H), 5.33 (d, J = 16.3 Hz, 1H), 3.69 (s, 3H), 3.46 (s, 3H), 3.10 (s, 3H).

e) (S)-2,3,4,5-Tetrahydro-7-[[[(4-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure of Example 45(e), methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (307.3 mg, 0.68 mmol) was saponified to afford the title compound (243.9 mg, 82%): MS (ES) m/e 436.2 $(M+H)^+$. Anal Calcd for $C_{23}H_{25}N_5O_4 \cdot 2.75\ H_2O$: C, 56.96; H, 6.34; N, 14.44: Found: C, 56.72; H, 6.27; N, 14.26.

Example 48

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5,7-dimethylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) 2-Amino-4,6-dimethyl-3-nitropyridine

2-Amino-4,6-dimethylpyridine (5.55 g, 45.43 mmol) was weighed into a 500 mL round bottomed flask. The flask was cooled to -78°C. Concentrated H_2SO_4 (25 mL, 450 mmol) was added, followed by concentrated HNO_3 (3.5 mL, 56.0 mmol). The mixture became a solid frozen mass. The cooling bath was removed and the reaction was allowed to warm to RT. After about 15 min there was an exothermic reaction with the release of some nitrous oxide gas, and the reaction became a very dark red color. The reaction was heated at 85 - 90°C for 3 hr, then was cooled to RT, diluted with ice, and neutralized with 6 N NaOH (160 mL). The aqueous solution was extracted with EtOAc (3 x), and the combined EtOAc layers were dried

($MgSO_4$), filtered, and evaporated under vacuum. The resulting yellowish-orange solid was adsorbed onto silica gel and flash chromatographed on a dry silica gel column. The column was eluted with 1:1 $CHCl_3/Et_2O$ to afford the title compound (1.0650 g, 14%): MS (ES) m/e 168.0 $(M+H)^+$.

b) 2,3-Diamino-4,6-dimethylpyridine

Following the procedure of Example 45(a), except substituting 2-amino-4,6-dimethyl-3-nitropyridine (1.0650 g, 6.37 mmol) for the 4-amino-3-nitrobenzotrifluoride, the title compound (836.1 mg, 95.7%) was prepared. This was used without characterization.

c) 4-Aza-2-[N-(benzyloxycarbonyl)-N-methyl]aminomethyl-5,7-dimethylbenzimidazole

Following the procedure of Example 45(b), except substituting 2,3-diamino-4,6-dimethylpyridine (836.1 mg, 6.09 mmol) for the 3,4-diaminobenzotrifluoride, the title compound (1.2273 g, 62%) following silica gel chromatography (3% $MeOH/CHCl_3$): MS (ES) m/e 325.0 $(M+H)^+$.

d) 4-Aza-2-(methylaminomethyl)-5,7-dimethylbenzimidazole

Following the procedure of Example 45(c), except substituting 4-aza-2-[N-(benzyloxycarbonyl)-N-methyl]aminomethyl-5,7-dimethylbenzimidazole (1.2273 g, 3.78 mmol) for the 2-[N-(benzyloxycarbonyl)-N-methyl]aminomethyl-5-trifluoromethylbenzimidazole, the title compound was obtained as a white powder following trituration with Et_2O. This material was used without characterization.

e) Methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5,7-dimethylbezimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Methyl (S)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (175.0 mg, 0.60 mmol) was weighed into a 100 mL round bottomed flask. CH_3CN (10 mL) was added, followed sequentially, by $HOBt \cdot H_2O$ (115.9 mg, 0.86 mmol), EDC (124.9 mg, 0.65 mmol), and diisopropylethylamine (0.13 mL, 0.75 mmol). A suspension of 4-aza-2-(methylaminomethyl)-5,7-dimethylbenzimidazole (144.5 mg, 0.76 mmol) and diisopropylethylamine (0.13 mL, 0.75 mmol) in CH_3CN was added, and the reaction was stirred at RT. After 22 hr, the reaction was evaporated under vacuum, and the residue was co-evaporated with toluene. Silica gel chromatography (3% $MeOH/CHCl_3$ (1 L) then 5%

MeOH/$CHCl_3$) gave the title compound (76.9 mg, 28%): MS (ES) m/e 465.2 $(M+H)^+$.

f) (S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5,7-dimethylbenzimidazol-2-yl)methyl]methylamino]carbonyl-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5,7-dimethylbezimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (76.9 mg, 0.17 mmol) was dissolved in MeOH (5 mL) and H_2O (5 mL), and 1.0 N NaOH (0.5 mL, 0.5 mmol) was added. After 24 hours at RT, the reaction was neutralized with 1.0 N HCl (0.5 mL), and the solvents were evaporated under vacuum. ODS chromatography (gradient: 5% CH_3CN/H_20 containing 0.1% TFA (500 mL), then 10% % CH_3CN/H_20 containing 0.1% TFA (500 mL), then 15% % CH_3CN/H_20 containing 0.1% TFA (500 mL), then 30% % CH_3CN/H_20 containing 0.1% TFA (500 mL)) gave a residue which was co-evaporated once with toluene and dried under high vacuum. The resulting residue was dissolved in MeOH (5 mL) and precipitated with Et_2O. The white solid was collected on a sintered glass funnel and dried in a vacuum desiccator overnight to yield the title compound (52.0 mg, 68%): HPLC (ODS column, 1.5 mL/min; gradient 5-50% CH_3CN/H_2O containing 0.1% TFA) t_R 12.38 min; MS (ES) m/e 451.2 $(M+H)^+$. Anal Calcd for $C_{23}H_{26}N_6O_4 \cdot 1\ H_2O \cdot 1\ CF_3CO_2H$: C, 51.55; H, 5.02; N, 14.43: Found: C, 51.34; H, 5.00; N, 14.41.

Example 49

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(5,6-difluorobenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) 1,2-Diamino-4,5-difluorobenzene

Following the procedure of Example 45(a), except substituting 4,5-difluoro-2-nitroaniline (2.0 g, 11.49 mmol) for the 4-amino-3-nitrobenzotrifluoride, the title compound was prepared. This was used without characterization.

b) 2-[N-(Benzyloxycarbonyl)-N-methyl]aminomethyl-5,6-difluorobenzimidazole

Following the procedure of Example 47(b), except substituting 1,2-diamino-4,5-difluorobenzene for the 1,2-diamino-3-methylbenzene, and running the AcOH cyclization step at 80°C instead of at 110°C, the title compound (1.3767 g, 36%) was

prepared: TLC Rf (1:1 CH_2Cl_2/Et_2O) 0.42; MS (ES) m/e 332.0 $(M+H)^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 7.50-7.14 (m, 8H), 5.13 (s, 2H), 4.61 (s, 2H), 3.06 (s, 3H).

c) 5,6-Difluoro-2-(methylaminomethyl)benzimidazole

Following the procedure of Example 46(b), except substituting 2-[N-(benzyloxycarbonyl)-N-methyl]aminomethyl-5,6-difluorobenzimidazole (1.3767 g, 4.16 mmol) for the 2-[N-(benzyloxycarbonyl)-N-methyl]aminomethyl-4,7-dimethoxybenzimidazole, the title compound (875.6 mg, quantitative) was prepared: MS (ES) m/e 198.0 $(M+H)^+$.

d) Methyl-(S)-2,3,4,5-tetrahydro-7-[[[5,6-difluorobenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Methyl (S)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (415.7 mg, 1.42 mmol) was taken up in CH_3CN, and HOBt · H_2O (209.3 mg, 1.55 mmol) and EDC (314.9 mg, 1.64 mmol) were added. After 5 min, and diisopropylethylamine (0.25 mL, 1.64 mmol) was added, which produced a clear, colorless solution. A solution of 5,6-difluoro-2-(methylaminomethyl)benzimidazole (284.5 mg, 1.44 mmol) in CH_3CN was added. After 30 minutes, the reaction became slightly turbid, so more diisopropylethylamine (0.25 mL) was added, which made the reaction again clear and colorless. After 24 hr, the reaction was evaporated under vacuum. The residue was co-evaporated once with toluene, then was chromatographed on silica gel ($CHCl_3$ (0.25 L), then 2% MeOH/$CHCl_3$ (1.5 L), then 5% MeOH/$CHCl_3$) to afford the title compound (456.8 mg, 68%): MS (ES) m/e 472.2 $(M+H)^+$; ^1H NMR (250 MHz, $CDCl_3$) δ 7.34-7.08 (m, 6H), 6.44 (br s, 1H), 5.39 (d, J = 16.2 Hz, 1H), 3.70 (s, 3H), 3.14 (s, 3H), 2.96 (s, 3H).

e) (S)-2,3,4,5-Tetrahydro-7-[[[(5,6-difluorobenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Methyl (S)-2,3,4,5-tetrahydro-7-[[[5,6-difluorobenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (456.8 mg, 0.97 mmol) was dissolved in MeOH (10 mL) and H_2O (10 mL). 1.0 N NaOH (3.0 mL, 3.0 mmol) was added and the reaction was stirred at RT. After 18 hr, the reaction was neutralized with 1.0 N HCl (3.0 mL). A white precipitate formed which was collected on a sintered glass filter and dried in a vacuum

desiccator. ODS chromatography (gradient: 10% CH_3CN/H_2O containing 0.1% TFA (500 mL), then 18% % CH_3CN/H_2O containing 0.1% TFA (500 mL), then 25% % CH_3CN/H_2O containing 0.1% TFA (500 mL)) gave a residue which was co-evaporated once with toluene. The resulting residue was dissolved in a small amount of MeOH and precipitated with Et_2O to give the title compound (330.9 mg) as a white powder: HPLC (ODS column; 1.5 mL/min; gradient 5-50% CH_3CN/H_2O containing 0.1% TFA) t_R = 14.12 min; MS (ES) m/e 458.2 $(M+H)^+$. Anal Calcd for $C_{22}H_{21}N_5O_4F_2 \cdot 2.5\ H_2O$: C, 52.57; H, 5.22; N, 13.94: Found: C, 52.76; H, 5.15; N, 13.67.

Example 50

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) Methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Methyl (S)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (228.8 mg, 0.78 mmol) was taken up in CH_3CN, and HOBt $\cdot H_2O$ (154.2 mg, 1.14 mmol), EDC (179.4 mg, 0.94 mmol), and diisopropylethylamine (0.50 mL, 0.94 mmol) were added sequentially. A solution of 2-(aminomethyl)-4-aza-5-methylbenzimidazole dihydrochloride (125.4 mg, 0.77 mmol) in CH_3CN /DMF was added, and the reaction was stirred at RT. After 24 hr, the reaction was evaporated under vacuum, and the residue was co-evaporated once with toluene. Silica gel chromatography ($CHCl_3$ (0.25 L) then 3% MeOH/$CHCl_3$ (0.5 L), then 5% MeOH/$CHCl_3$) gave the title compound (159.9 mg, 48%): MS (ES) m/e 437.2 $(M+H)^+$.

b) (S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure of Example 48(f), methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (159.9 mg, 0.37 mmol) was saponified and purified to afford the title compound: MS (ES) m/e 423.39 $(M+H)^+$. Anal. Calcd for $C_{21}H_{22}N_6O_4 \cdot 0.5\ H_2O \cdot 1.25$ TFA: C, 52.64; H, 5.02; N, 16.74. Found: C, 52.65; H, 5.02; N, 16.74.

Example 51

Preparation of (S)-2,3,4,5-tetrahydro-4-methyl-7-[[[(4-nitrobenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) 2-[N-(tert-Butoxycarbonyl)-N-methyl]aminomethyl-4-nitrobenzimidazole

Boc-sarcosine (2.0320 g, 10.74 mmol) was dissolved in dry THF and cooled in a dry-ice/acetone bath to -15°C. Triethylamine (5.0 mL, 3.6375 mmol) was added, followed by isobutylchloroformate (1.5 mL, 11.56 mmol). After 0.5 hr, the mixture was added to a solution of 1,2-diamino-3-nitrobenzene (1.3047 g, 10.77 mmol) in dry THF at -20°C, and the reaction was allowed to warm to RT. After 24 hr, the reaction was evaporated under vacuum and the residue was partitioned between EtOAc and 1.0 N $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organics were dried ($MgSO_4$), filtered, and evaporated under vacuum. The residue was dissolved in glacial AcOH (100 mL), and the solution was heated at 75°C. After 24 hr, the reaction was evaporated under vacuum, and the residue was co-evaporated with toluene (2 x). The material was adsorbed onto silica gel and flash chromatographed on a dry silica gel column (gradient: $CHCl_3$ (0.5 L), then 2% MeOH/$CHCl_3$ (1 L), then 5% MeOH/$CHCl_3$) to afford the title compound (2.2089 g, 75%): ^1H NMR (250 MHz, $CDCl_3$) δ 8.10 (dd, 2H), 7.40-7.32 (m, 1H), 4.69 (s, 2H), 3.02 (s, 3H), 1.54 (s, 9H).

b) 2-(Methylaminomethyl)-4-nitrobenzimidazole

2-[N-(tert-Butoxycarbonyl)-N-methyl]aminomethyl-4-nitrobenzimidazole (2.2089 g, 8.05 mmol) was treated with 4 N HCl in dioxane at RT. After the addition, there was an immediate precipitation of a white solid. After 4 hr, the reaction was evaporated under vacuum and the residue was triturated with diethyl ether to give the title compound (1.639 g) as a white solid. This was used without characterization.

c) Methyl-(S)-2,3,4,5-tetrahydro-7-[[[(4-nitrobenzimidazol-2-yl)methyl]methylamino]carbonyl-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Following the procedure of Example 49(d), except substituting 2-(methylaminomethyl)-4-nitrobenzimidazole for 5,6-difluoro-2-(methylaminomethyl)benzimidazole, the title compound (292.9 mg, quantitative) was prepared: MS(ES) m/e 481.2 $(M+H)^+$.

d) (S)-2,3,4,5-Tetrahydro-7-[[[(4-nitrobenzimidazol-2-yl)methyl]methylamino]carbonyl-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure of Example 45(e), methyl (S)-2,3,4,5-tetrahydro-7-[[[(4-nitrobenzimidazol-2-yl)methyl]methylamino]carbonyl-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (292.9 mg, 0.61 mmol) was saponified to afford the title compound (211.0 mg, 68%): MS (ES) m/e 467.4 $(M+H)^+$. Anal. Calcd for $C_{22}H_{22}N_6O_6 \cdot 2.5\ H_2O$: C, 52.12; H, 5.27; N, 16.58: Found: C, 52.07; H, 4.97; N, 16.40.

Example 52

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(4-aminobenzimidazol-2-yl)methyl]methylamino]carbonyl-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) (S)-2,3,4,5-tetrahydro-7-[[[(4-aminobenzimidazol-2-yl)methyl]methylamino]carbonyl-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

(S)-2,3,4,5-Tetrahydro-7-[[[(4-nitrobenzimidazol-2-yl)methyl]methylamino]carbonyl-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid (108.7 mg, 0.21 mmol) was dissolved in MeOH, and a catalytic amount of 10% Pd/C was added. The reaction was purged with H_2, then was stirred at RT under H_2 (balloon). After 20 hr, the catalyst was removed by filtration through celite®, and the filtrate was evaporated under vacuum. The resulting solid was dissolved in MeOH, reprecipitated with Et_2O, dried in a vacuum desiccator, and purified by ODS chromatography (gradient: H_2O containing 0.1% TFA (500 mL), then 5% CH_3CN/H_2O containing 0.1% TFA (500 mL), then 10% % CH_3CN/H_2O containing 0.1% TFA (500 mL), then 15% % CH_3CN/H_2O containing 0.1% TFA (500 mL), then 20% % CH_3CN/H_2O containing 0.1% TFA (500 mL), then 25% % CH_3CN/H_2O containing 0.1% TFA (500 mL), then 30% % CH_3CN/H_2O containing 0.1% TFA (500 mL)). The resulting material was co-evaporated once with toluene then was triturated with diethyl ether to afford the title compound (34.7 mg): MS (ES) m/e 437.5 $(M+H)^+$; Anal. Calcd for $C_{22}H_{24}N_6O_4 \cdot 1.5\ H_2O \cdot 1.5$ TFA: C, 47.32; H, 4.53; N. 13.24: Found: C, 47.35, H, 4.86; N. 13.61.

Example 53

Preparation of 2,3,4,5-tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid

a) 2-[1(R)-[N-(Benzyloxycarbonyl)-N-methyl]aminoethyl]benzimidazole

Following the procedure of Example 47(b), except substituting Cbz-N-methyl-D-alanine for the Cbz-sarcosine, and substituting 1,2-phenylenediamine for the 1,2-diamino-3-methylbenzene, and running the AcOH cyclization step at 80°C instead of at 110°C, the title compound was prepared: MS (ES) m/e 310.2 $(M+H)^+$.

b) 2-[1(R)-(Methylaminoethyl)]benzimidazole

Following the procedure of Example 46(b), except substituting 2-[1(R)-[N-(benzyloxycarbonyl)-N-methyl]aminoethyl]benzimidazole for the 2-[N-(benzyloxycarbonyl)-N-methyl]aminomethyl-4,7-dimethoxybenzimidazole, the title compound (276.0 mg, 48%) was prepared: MS(ES) m/e 176.2 $(M+H)^+$.

c) Methyl 2,3,4,5-tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Following the procedure of Example 49(d), except substituting 2-[1(R)-(methylaminoethyl)]benzimidazole for the 5,6-difluoro-2-(methylaminomethyl)benzimidazole, the title compound (203.5 mg, 90%) was prepared: MS (ES) m/e 450.5 $(M+H)^+$.

d) 2,3,4,5-Tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure of Example 49(e), methyl 2,3,4,5-tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate was saponified to afford the title compound (179.3 mg, 75%) following ODS chromatography: MS (ES) m/e 436 5 $(M+H)^+$. Anal. Calcd for $C_{23}H_{25}N_5O_4 \cdot 0.75\ H_2O \cdot 0.75$ TFA: C, 55.01; H, 5.14; N, 13.10; Found: C, 54.98; H, 5.42; N. 12.75.

Example 54

Preparation of ethyl (S)-2,3,4,5-tetrahydro-7-[[[(4-Aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

a) Ethyl (S)-2,3,4,5-tetrahydro-7-[[[(4-Aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1.4-benzodiazepine-2-acetate

(S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid (0.5 g) was dissolved in EtOH, and the solution was cooled in an ice bath to 0°C. Gaseous HCl was bubbled into the solution until the solution was saturated, then the flask was sealed with a rubber septum and the cooling bath was removed. The reaction was stirred at RT for 20 hr, then the solvents were evaporated under vacuum. The residue was co-evaporated three times with toluene (3 x), then was dissolved in EtOH and precipitated with Et_2O. The solid was collected on a sintered glass funnel and dried in a vacuum desiccator overnight to afford the title compound (483.9 mg): MS (ES) m/e 451.4 $(M+H)^+$. Anal. Calcd for $C_{23}H_{26}N_6O_4 \cdot HCl \cdot 1.375\ H_2O$: C, 53.98; H, 5.86; N, 16.42. Found: C, 54.00; H, 5.82; N, 16.42.

Example 55

Preparation of 2,3,4,5-tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid

a) 2-[1(S)-[N-(tert-Butoxycarbonyl)-N-methyl]aminoethyl]benzimidazole

Following the procedure of Example 51(a) except substituting Boc-N-methyl-L-alanine for the Boc-sarcosine, and substituting 1,2-phenylenediamine for the 1,2-diamino-3-nitrobenzene, the title compound (1.7792 g, 65%) was prepared following recrystallization from $CHCl_3$/hexanes: MS (ES) m/e 276.4 $(M+H)^+$.

b) 2-[1(S)-(Methylaminoethyl)]benzimidazole

Following the procedure of Example 51(b), except substituting 2-[1(S)-[N-(tert-butoxycarbonyl)-N-methyl]aminoethyl]benzimidazole for the 2-[N-(tert-butoxycarbonyl)-N-methyl]aminomethyl-4-nitrobenzimidazole, the title compound was prepared. This was used without characterization.

c) Methyl (S)-2,3,4,5-tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Following the procedure of Example 49(d), except substituting 2-[1(S)-(methylaminoethyl)]benzimidazole for the 5,6-difluoro-2-(methylaminomethyl)benzimidazole, the title compound (414.7 mg, 88%) was prepared: MS (ES) m/e 450.2 $(M+H)^+$.

d) 2,3,4,5-Tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure of Example 45(e), methyl (S)-2,3,4,5-tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate was saponified to afford the title compound (117.2 mg): MS (ES) m/e 436.2 $(M+H)^+$. Anal Calcd for $C_{23}H_{25}N_5O_4 \cdot 0.75\ H_2O \cdot 0.75$ TFA: C, 55.05; H, 5.14; N, 13.10; Found: C, 55.14; H, 5.38; N, 13.04.

Example 56

Preparation of 2,3,4,5-tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid

a) 2-[1(S)-(tert-Butoxycarbonyl)aminoethyl]benzimidazole

Following the procedure of Example 51(a) except substituting Boc- L-alanine for the Boc-sarcosine, and substituting 1,2-phenylenediamine for the 1,2-diamino-3-nitrobenzene, the title compound (714.7 mg, 25%) was prepared: MS (ES) m/e 262.4 $(M+H)^+$.

b) 2-[1(S)-(Aminoethyl)]benzimidazole

Following the procedure of Example 51(b), except substituting 2-[1(S)-(tert-butoxycarbonyl)aminoethyl]benzimidazole for the 2-[N-(tert-butoxycarbonyl)-N-methyl]aminomethyl-4-nitrobenzimidazole, the title compound was prepared. This was used without characterization.

c) Methyl 2,3,4,5-tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl)]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Following the procedure of Example 49(d), except substituting 2-[1(S)-(aminoethyl)]benzimidazole for 5,6-difluoro-2-(methylaminomethyl)benzimidazole, the title compound (270.7 mg, 80%) was prepared: MS (ES) m/e 436.0 $(M+H)^+$.

d) 2,3,4,5-Tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl)]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure of Example 45(e), methyl 2,3,4,5-tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl)]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate was saponified to afford the title compound (158.1 mg, 61%): MS (ES) m/e 422.0 $(M+H)^+$. Anal. Calcd for $C_{22}H_{23}N_5O_4 \cdot 1.75\ H_2O$: C, 58.37; H, 5.90; N, 15.46; Found: C 58.17; H, 5.77; N, 15.08.

Example 57

Preparation of 2,3,4,5-tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid

a) 2-[1(R)-(Benzyloxycarbonyl)aminoethyl]benzimidazole

Following the procedure of Example 47(b), except substituting Cbz-D-alanine for the Cbz-sarcosine, and substituting 1,2-phenylenediamine for the 1,2-diamino-3-methylbenzene, and running the AcOH cyclization step at 80°C instead of at 110°C, the title compound (1.1455 g, 43%) was prepared: MS (ES) m/e 296.4 $(M+H)^+$.

b) 2-(1(R)-Aminoethyl)benzimidazole

Following the procedure of Example 46(b), except substituting 2-[1(R)-(benzyloxycarbonyl)aminoethyl]benzimidazole for the 2-[N-(benzyloxycarbonyl)-N-methyl]aminomethyl-4,7-dimethoxybenzimidazole, the title compound (258.1 mg, 93%) was prepared: MS(ES) m/e 161.9 $(M+H)^+$.

c) Methyl 2,3,4,5-tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetate

Following the procedure of Example 49(d), except substituting 2-(1(R)-aminoethyl)benzimidazole for the 5,6-difluoro-2-(methylaminomethyl)benzimidazole, the title compound (263.6 mg, 84%) was prepared: MS (ES) m/e 436.3 $(M+H)^+$.

d) 2,3,4,5-Tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Following the procedure of Example 49(e), methyl 2,3,4,5-tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetate was saponified to afford the title compound (125.0 mg, 49%): MS (ES) m/e 422.0 $(M+H)^+$. Anal. Calcd for $C_{22}H_{23}N_5O_4 \cdot 0.5\ H_2O \cdot 1.25$ HCl: C, 55.51; H, 5.35; N, 14.71. Found: C, 55.70; H, 5.47; N, 14.53.

Example 58

Preparation of (S)-2,3,4,5-tetrahydro-7-[[[(imidazo(1,2a)pyrid-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) 2-Carboethoxyimidazo[1,2a]pyridine

2-Aminopyridine (4 g, 42.50 mmol) was dissolved in MeOH (50 mL). Ethyl bromopyruvate (8.3 g, 42.50 mmol) was added and the reaction was stirred at 70°C for 2 hr. The solvent was then eliminated and the solution was neutralized with 1 M NaOH. The reaction was extracted with EtOAc, and the combined EtOAc layers were washed with brine. Drying ($MgSO_4$), filtration, concentration, and silica gel flash column chromatography (2% MeOH/Cl_2CH_2) gave the title compound (4.5 g, 56%) as a pale yellow solid: ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, J = 7 Hz, 3H), 4.45 (q, J = 7 Hz, 2H), 6.86 (t, J = 6.6 Hz, 1H), 7.24 (t, J = 6.6 Hz, 1H).

b) 2-Hydroxymethylimidazo[1,2a]pyridine

2-Carboethoxyimidazo[1,2a]pyridine (0.5 g, 2.81 mmol) was dissolved in dry THF at 0°C, and then a solution of lithium aluminum hydride (0.5 mL of a 1.0 M in THF) was added. The reaction was allowed to warm to RT and stirred for 1 hr. H_2O (0.2 mL) was added, followed by 15% NaOH (0.2 mL), and finally H_2O (0.6 mL). The solids were removed by filtration and washed with hot THF (2 x 100 mL) and hot $CHCl_3$ (4 x 100 mL). The filtrate and washings were combined and dried ($MgSO_4$). Following filtration the solvents were removed under reduce pressure the residue was purified by silica gel flash column chromatography (5% MeOH/Cl_2CH_2) to obtain the title compound (0.1 g, 25%) as pale yellow liquid: ^1H NMR (400 MHz, $CDCl_3$) δ 4.85 (s, 2H), 6.76 (t, J = 6.8 Hz, 1H), 7.15 (t, J = 6.8 Hz, 1H), 7.53 (s, 1H), 7.54 (d, J = 6.7 Hz, 1H), 8.1 (d, J = 6.7 Hz, 1H). MS (ES) m/e 149 $(M + H)^+$.

c) 2-Chloromethylimidazo[1,2a]pyridine

Thionyl chloride (0.4 mL, 3.2 mmol) was added to a solution of 2-hydroxymethylimidazo[1,2a]pyridine (0.4 g, 2.7 mmol) in $CHCl_3$ (30 mL) at 0°C.. After stirring at RT for 1 hr, the suspension was poured into a mixture of ice, 10% $NaHCO_3$, and $CHCl_3$. The layers were separated, and the aqueous phase was extracted with $CHCl_3$. The organic extracts were combined and dried ($MgSO_4$). Following filtration, the solvents were removed under reduce pressure to obtain the title compound (0.4 g, 89%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.7 (s, 2H), 6.7 (t, 1H), 7.2 (t, 1H), 7.5 (d, 1H), 7.6 (s, 1H), 8.0 (d, 1H); MS (ES) m/e 167 $(M + H)^+$.

d) 2-(Methylaminomethyl)imidazo[1,2a]pyridine

Freshly condensed methylamine (15 mL) was added to a solution of 2-chloromethylimidazo[1,2a]pyridine (317 mg, 2 mmol) in EtOH (5 mL) at 0°C, and the reaction mixture was allowed to stir at 0°C for 2 h. The solvent was then eliminated and the residue was purified by reverse-phase column chromatography (C-18 silica gel, H_2O containing 0.1 % TFA). Lyophilization gave the title compound (461 mg, 87%) as a white solid: ^1H NMR (250 MHz, $CDCl_3$) δ 2.5 (s, 3H), 4.0 (s, 2H), 6.7 (t, 1H), 7.2 (t, 1H), 7.5 (d, 1H), 7.6 (s, 1H), 8.1 (d, 1H). MS (ES) m/e 162 $(M + H)^+$.

e) Methyl (S)-2,3,4,5-tetrahydro-7-[[[(imidazo(1,2a)pyrid-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

Methyl (S)-7-carboxy-4-methyl-3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine-2-acetate (828.2 mg, 2.83 mmol) was taken up in CH_3CN, and HOBt · H_2O (398.1 mg, 2.92 mmol), EDC (562.9 mg, 2.94 mmol), and diisopropylethylamine (1 mL, 5.74 mmol) were added sequentially. When the solids had dissolved, a solution of 2-(methylaminomethyl)imidazo[1,2a]pyridine (460.7 mg, 2.86 mmol) and diisopropylethylamine (1.5 mL, 8.61 mmol) in CH_3CN was added, and the reaction was stirred at RT. After 24 hr, the reaction was concentrated, and the residue was co-evaporated with toluene (2 x). The resulting residue was chromatographed on silica gel (5% MeOH/$CHCl_3$) to give the title compound (694.6 mg, 56%): MS (ES) m/e 436.4 $(M+H)^+$.

f) (S)-2,3,4,5-Tetrahydro-7-[[[(imidazo(1,2a)pyrid-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

Methyl (S)-2,3,4,5-tetrahydro-7-[[[(imidazo(1,2a)pyrid-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

(663.4 mg, 1.52 mmol) was dissolved in MeOH (10 mL). H_2O (10 mL) was added, followed by 1.0 N NaOH (5 mL, 5.0 mmol), and the reaction was stirred at RT. After 20 hr, the reaction was neutralized with 1.0 N HCl (5 mL), and the solution was evaporated under vacuum. The residue was purified by ODS chromatography (gradient: H_2O containing 0.1% TFA (500 mL), then 5% CH_3CN/H_2O containing 0.1% TFA (500 mL), then 10% CH_3CN/H_2O containing 0.1% TFA (500 mL), then 15% CH_3CN/H_2O containing 0.1% TFA (500 mL), then 20% CH_3CN/H_2O containing 0.1% TFA (500 mL)) followed by rechromatography on ODS (gradient: H_2O containing 0.1% TFA (250 mL), then 10% CH_3CN/H_2O containing 0.1% TFA (1.5 L), then 20% CH_3CN/H_2O containing 0.1% TFA (1 L). Fractions containing pure material were combined and concentrated. The residue was co-evaporated with toluene, then was dissolved in MeOH and reprecipitated with Et_2O to afford the title compound (96.4 mg): MS (ES) m/e 421.9 $(M+H)^+$. Anal. Calcd for $C_{22}H_{23}N_5O_4 \cdot 0.25\ H_2O \cdot$ TFA: C, 53.38; H, 4.57; N, 12.97. Found: C, 53.68; H, 4.97; N, 12.94.

Example 59

Preparation of (±)-7-[[[(4,5-Dimethyl-1H-imidazol-2-yl)methyl]methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

a) N-(Carbobenzyloxy)-N-(methyl)acetonitrile

Cbz chloride (7.40 mL, 49.3 mmol) was added slowly at RT to a solution of N methylaminoacetonitrile hydrochloride (5.0 g, 46.92 mmol) and triethylamine (13.4 mL, 96.2 mmol) in dichloromethane (200 mL). The reaction was stirred at RT 18 h, and the mixture was washed with 1N HCl, water and brine. The organic layer was dried ($MgSO_4$) and concentrated to yield the title compound (6.97 g, 73%) as a clear oil.

b) N-(Carbobenzyloxy)-N-(methyl)aminothioacetamide

Hydrogen sulfide was bubbled through a solution of N-(carbobenzyloxy)-N-(methyl)acetonitrile (15 g, 73.5 mmol) and triethylamine (30.75 mL, 220.6 mmol) in DMF (250 mL). After 20 min, the flask was closed and the reaction was stirred at RT for 18 h. The reaction was then poured into 2 N $NaHCO_3$ (1 L) and extracted with dichloromethane. The combined organic phase was washed with 1:1

water/brine (5 x), dried ($MgSO_4$), and concentrated to give a yellow oil which was purified by silica gel flash chromatography (step gradient, 40-50% ethyl acetate/hexane) to yield the title compound (12.26 g, 70%) as a white solid: MS (ES) m/e 239.0 $[M+H]^+$.

c) N-(Carbobenzyloxy)-N-methyl-S-(methyl)acetothioimidate

Iodomethane (17.66 mL, 283.6 mmol) was added at RT to a solution of N-(carbobenzyloxy)-N-(methyl)aminothioacetamide(6.75 g, 28.36 mmol) in acetone 100 mL). The solution was stirred at RT in the dark for 3 h, and the resulting precipitate was filtered to yield the title compound (9.63 g, 89%) as a white solid: MS (ES) m/e 253.4 $[M+H]^+$.

d) (±)-2-Amino-3,3-dimethoxybutane

Sodium cyanoborohydride was added to a solution of 3,3-dimethoxy-2-butanone (1.32 g, 10 mmol) and ammonium acetate (1.1 g, 100 mmol) in methanol (30 mL). The pH was adjusted to 6 with methanolic HCl, and the reaction was stirred at RT overnight and concentrated. The residue was dissolved in water, and the pH was adjusted to 5 with aqueous HCl. The resulting solution was extracted with ether (3 x), and the aqueous phase was basified to pH 10 with Na_2CO_3, and extracted with ether. The organic layer was dried ($MgSO_4$) and concentrated to yield the title compound (1.1 g, 83%) as a clear oil: MS (ES) m/e134.2 [M+H]+.

e) N-(Carbobenzyloxy)-N-methyl-(4,5-dimethyl-1H-imidazol-2-yl)methanamine

A solution of (±)-2-amino-3,3-dimethoxybutane (1.05 g, 7.89 mmol) and N-(carbobenzyloxy)-N-methyl-S-(methyl)acetothioimidate (2.0 g, 5.26 mmol) in methanol (30 mL) was warmed at 60°C for 2 h, and concentrated to give a yellow oil. The crude oil was dissolved in 6 N HCl (30 mL) and stirred at RT 1 h. The solution was basified to pH 12 with aqueous NaOH and then extracted with dichloromethane. The combined organic phase was dried ($MgSO_4$) and concentrated to give a brown oil which was purified by silica gel flash chromatography (4% methanol/dichloromethane) to yield the title compound (0.590 g, 41%) as a clear oil: MS (ES) m/e 274.0 $[M+H]^+$.

f) N-Methyl-(4,5-dimethyl-1H-imidazol-2-yl)methanamine

A solution of N-(carbobenzyloxy)-N-methyl-(4,5-dimethyl-1H-imidazol-2-yl)methanamine (0.35 g, 1.28 mmol) in methanol (15 mL) and glacial acetic acid (5

mL), containing 10% Pd/C (0.035 g), was shaken in a H_2 atmosphere (45 Psi) for 6 h. The reaction was filtered and filtrate concentrated to give the title compound (0.22 g, 86%) as a brown oil which was used in the next step without further purification: MS (ES) m/e 140 $[M+H]^+$.

g) Methyl (±)-7-[[[(4,5-dimethyl-1H-imidazol-2-yl)methyl]methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate

A solution of N-methyl-(4,5-dimethyl-1H-imidazol-2-yl)methanamine (0.20 g, 1.1 mmol) and methyl (±)-7-carboxy-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.320 g, 1.1 mmol) in the presence of DIEA (0.287 mL, 1.65 mmol) was stirred at RT. EDC (0.316 g, 1.65 mmol) was then added, followed by DMAP (0.013 g, 0.11 mmol). The mixture was stirred at RT for 18 h, and concentrated to give an oil which was purified by silica gel flash chromatography (step gradient, 0.5-2% methanol/dichloromethane) to yield the title compound (0.060 g, 9%) as a clear oil: MS (ES) m/e 414.2 $[M+H]^+$.

h) (±)-7-[[[(4,5-Dimethyl-1H-imidazol-2-yl)methyl]methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid

1 N Sodium hydroxide (3 eq) was added to a solution of methyl (±)-7-[[[(4,5-dimethyl-1H-imidazol-2-yl)methyl]methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate (0.060g, 0.145 mmol), the mixture was stirred at RT for 5 h, and concentrated. The residue was dissolved in water and the pH was adjusted to 5 with 50% acetic acid. The solution was concentrated and purified by MPLC (ODS-AQ, 10% acetonitrile/water containing 0.1% TFA, UV detection at 220 nm) to yield the title compound (0.050 g, 86%) as a white solid: MS (ES) m/e 400.2 $[M+H]^+$.

Example 60

Preparation of 3-[[3-[2-(benzimidazol-2-yl)ethyl]isoxazolin-5(R,S)-yl]acetyl]amino-3(R,S)-methylpropanoic acid

a) 4-(Benzimidazol-2-yl)-1-butene

According to the general procedures of Preparation 4 in P50256-1, except substituting 4-pentenoic acid for the Boc-sarcosine, the title compound is prepared.

b) 4-(1-Toluenesulfonylbenzimidazol-2-yl)-1-butene

Sodium hydride is added carefully to a solution of 4-(benzimidazol-2-yl)-1-butene (50 mmole) and 4-toluenesulfonyl chloride (55 mmole) in dry THF (200 mL). The reaction is stirred at RT until complete, then is quenched with saturated NH_4Cl (200 mL), and the mixture is extracted with EtOAc. The combined organic extracts are dried ($MgSO_4$) and concentrated, and the residue is purified by silica gel chromatography to give the title compound.

c) 4-(1-Toluenesulfonylbenzimidazol-2-yl)-1-butanal

Ozone is bubbled into a solution of 4-(1-toluenesulfonylbenzimidazol-2-yl)-1-butene (40 mmole) in CH_2Cl_2 (160 mL) and MeOH (40 mL) at -78°C until the blue color persists, then the excess ozone is removed by bubbling argon through the solution. Dry dimethylsulfide (excess) is added, and the reaction is warmed to RT. The reaction is stirred at RT until complete, then is concentrated, and the residue is chromatographed on silica gel to afford the title compound.

d) 4-(1-Toluenesulfonylbenzimidazol-2-yl)-1-butanal oxime

Hydroxylamine hydrochloride (33 mmole) is added to a solution of 4-(1-toluenesulfonylbenzimidazol-2-yl)-1-butanal (30 mmole) and anhydrous sodium acetate (66 mmole) in MeOH (150 mL) at 0°C. The reaction is stirred at 0°C until complete, then is concentrated, and the residue is partitioned between H_2O and EtOAc. The layers are separated, and the aqueous layer is extracted with EtOAc. The combined organic layers are washed sequentially with 5% $NaHCO_3$ and saturated brine, dried ($MgSO_4$), and concentrated to afford the title compound.

e) 4-(1-Toluenesulfonylbenzimidazol-2-yl)-1-butanoximinoyl chloride

According to the procedure of Example 1(b) in WO 95/14682, except substituting 4-(1-toluenesulfonylbenzimidazol-2-yl)-1-butanal oxime for the 4-cyanobenzoxime, the title compound is prepared.

f) tert-Butyl [3-[2-(1-toluenesulfonylbenzimidazol-2-yl)ethyl]isoxazolin-5(R,S)-yl]acetate

According to the procedure of Example 1(d) of WO 95/14682, except substituting 4-(1-toluenesulfonylbenzimidazol-2-yl)-1-butanoximinoyl chloride for the 4-cyanobenzoximinoyl chloride, and substituting tert-butyl 3-butenoate for the methyl 3-butenoate, the title compound is prepared.

g) [3-[2-(1-Toluenesulfonylbenzimidazol-2-yl)ethyl]isoxazolin-5(R,S)-yl]acetic acid

4 M HCl in dioxane (10 mL) is added to a solution of tert-butyl [3-[2-(1-toluenesulfonylbenzimidazol-2-yl)ethyl]isoxazolin-5(R,S)-yl]acetate (5 mmole) in CH_2CH_2 (40 mL) at 0°C. The reaction is stirred at RT until complete, then is concentrated to afford the title compound.

h) Ethyl 3-[[3-[2-(1-toluenesulfonylbenzimidazol-2-yl)ethyl]isoxazolin-5(R,S)-yl]acetyl]amino-3(R,S)-methylpropanoate

EDC (1.2 mmole) is added to a solution of [3-[2-(1-toluenesulfonylbenzimidazol-2-yl)ethyl]isoxazolin-5(R,S)-yl]acetic acid (1 mmole), ethyl 3(R,S)-aminobutyrate (1.2 mmole), HOBt · H_2O (1.2 mmole), and diisopropylethylamine (4 mmole) in anhydrous CH_3CN (5 mL) at RT. The reaction is stirred at RT until complete, then is concentrated, and the residue is purified by silica gel chromatography to afford the title compound.

i) 3-[[3-[2-(Benzimidazol-2-yl)ethyl]isoxazolin-5(R,S)-yl]acetyl]amino-3(R,S)-methylpropanoic acid

1.0 N LiOH (2.5 mmole) is added to a solution of ethyl 3-[3-[2-(1-toluenesulfonylbenzimidazol-2-yl)ethyl]isoxazolin-5(R,S)-yl]acetyl]amino-3(R,S)-methylpropanoate (0.5 mmole) in THF (2.5 mL). The reaction is stirred at RT until complete, then is neutralized with 1.0 N HCl. The solution is concentrated and the residue is purified by reverse-phase chromatography to afford the title compound.

Example 61

Preparation of 3-[3,4-dihydro-8-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-1-methyl-2,5-dioxo-1H-1,4-benzodiazepine]-4-propanoic acid

a) 2-Amino-4-iodobenzoic acid

The title compound is prepared from the oxidation of 4-iodo-2-nitrotoluene to give 4-iodo-2-nitrobenzoic acid according to the method of Sasson, et al., *J. Org. Chem.* **1986**, *51*, 2880-2883, followed by reduction of the nitro group using iron and acetic acid.

b) 4-Iodoisatoic anhydride

To a mechanically stirred ice-cold solution of 2-amino-4-iodobenzoic acid (26.3 g, 0.1 mol), sodium carbonate (10.6 g, 0.1 mol) and water (250 mL), is slowly added, via an addition funnel, a solution of phosgene in toluene (80 mL of 1.93 M solution). After 2 h, the precipitated product is isolated by filtration and the solid is washed successively with water (200 mL), a 1:1 mixture of ethanol/ether (300 mL),and ether (200 mL). Drying under vacuum yields the title compound.

c) N-(2-Amino-4-iodobenzoyl)-β-alanine benzyl ester

A magnetically stirred solution of 4-iodoisatoic anhydride (5.0 g, 0.0173 mol), β alanine benzyl ester tosylate (5.85 g, 0.0173 mol), and dimethylaminopyridine (0.5 g, 0.0041 mol) in pyridine (35 mL) is heated for 2 h at 80°C. The reaction mixture is allowed to cool to RT and concentrated in vacuo. The resulting residue is dissolved in ethyl acetate (100 mL), and washed successively with 10% cupric sulfate (2 x 50 mL), saturated sodium bicarbonate (1 x 50 mL) and brine (1 x 50 mL). Drying (Na_2SO_4), filtration, concentration, and silica gel chromatography (1:1 EtOAc/hexanes) gives the title compound.

d) N-(4-Iodo-2-methylaminobenzoyl)-β-alanine benzyl ester

A magnetically stirred solution of N-(2-amino-4-iodobenzoyl)-β-alanine benzyl ester (2.0 mmol), 2,6-lutidine (0.35 mL, 3.0 mmol) and methyl iodide (0.19 mL, 3.0 mmol) in DMF (15 mL) is heated at 50°C for 15 h. The reaction mixture is allowed to cool to RT and concentrated in vacuo. The resulting residue is dissolved in ethyl acetate (75 mL), and washed successively with 10% citric acid (1 x 50 mL), saturated sodium bicarbonate (1 x 50 mL) and brine (1 x 50 mL). Drying (Na_2SO_4), filtration, concentration, and silica gel chromatography (gradient 35-65 % EtOAc/hexanes) gives the title compound.

e) Benzyl 3-[3,4-dihyro-8-iodo-1-methyl-2,5-dioxo-1H-1,4-benzodiazepine]-4-propanoate

To a cold (-30°C) magnetically stirred solution of N-(4-iodo-2-methylaminobenzoyl)-β-alanine benzyl ester (0.305 g, 0.69 mmol) and triethylamine (0.144 g, 1.04 mmol) in methylene chloride (3 mL) is added slowly a solution of α-bromoacetyl bromide (0.09 mL, 1.04 mmol) in methylene chloride (2 mL) under argon. The reaction mixture is allowed to warm to RT and stir for 2 h. The mixture is diluted with methylene chloride (40 mL) and washed successively with 10% citric acid (1 x 50 mL) and saturated sodium bicarbonate (1 x 50 mL), dried (Na_2SO_4),

filtered and concentrated in vacuo. The resulting residue is dissolved in DMF (3 mL) and added via an addition funnel to a slurry of sodium hydride (25 mg, 1.04 mmol) in DMF (2 mL) which is cooled to 0°C. After 2 h of stirring, the mixture is poured over an ice cooled solution of 10% citric acid (50 mL) and extracted with ethyl acetate (3 x 40 mL). The combined extracts are washed with saturated sodium bicarbonate (1 x 50 mL), dried (Na_2SO_4), filtered and concentrated. Silica gel chromatography (gradient 40-70% EtOAc/hexanes) gives the title compound.

f) Benzyl-3-[3,4-dihyro-8-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-1-methyl-2,5-dioxo-1H-1,4-benzodiazepine]-4-propanoate

A mixture of benzyl 3-[3,4-dihyro-8-iodo-1-methyl-2,5-dioxo-1H-1,4-benzodiazepine]-4-propanoate(2 mmol), 2-(methylaminomethyl)benzimidazole dihydrochloride (3 mmol), DIEA (1.8 mL, 10 mmol), and $(Ph_3P)_2PdCl_2$ (140 mg, 0.2 mmol) in N-methyl-2-pyrrolidinone (20 mL) is heated to 110°C under CO balloon for 3 h. The mixture is then concentrated and the residue is purified by silica gel flash chromatography to give the title compound.

g) 3-[3,4-Dihydro-8-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-1-methyl-2,5-dioxo-1H-1,4-benzodiazepine]-4-propanoic acid

A mixture of benzyl-3-[3,4-dihyro-8-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-1-methyl-2,5-dioxo-1H-1,4-benzodiazepine]-4-propanoate (2 mmol) and 10% Pd/C (0.02 g) in ethanol (100 mL) is hydrogenated in an atmosphere of H_2 (50 psi) for 6 h. The catalyst is removed by filtration, and the filtrate is concentrated under vacuo to afford the title compound.

Example 62

Preparation of 3-[4H-imidazo[1,2-a][1,4]benzodiazepine-5(6H)-1-methyl-6-oxo-9-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]]-4-propanoic acid

a) Ethyl N-(2-amino-4-iodobenzoyl)-β-alanine

A magnetically stirred solution of 4-iodoisatoic anhydride (0.0173 mol), β alanine ethyl ester hydrochloride (0.0173 mol), and dimethylaminopyridine (0.5 g, 0.0041 mol) in pyridine (35 mL) is heated for 2 h at 80°C. The reaction mixture is allowed to cool to RT and concentrated in vacuo. The resulting residue is dissolved in ethyl acetate (100 mL), and washed successively with 10% cupric sulfate (2 x 50

mL), saturated sodium bicarbonate (1 x 50 mL) and brine (1 x 50 mL). Drying (Na_2SO_4), filtration, concentration, and silica gel chromatography (1:1 EtOAc/hexanes) gives the title compound.

b) Ethyl-3-[3,4-dihyro-8-iodo-2,5-dioxo-1H-1,4-benzodiazepine]-4-propanoate

To a cold (-30°C) magnetically stirred solution of ethyl N-(2-amino-4-iodobenzoyl)-β-alanine (0.69 mmol), and triethylamine (0.144 g, 1.04 mmol) in methylene chloride (3 mL) is added slowly a solution of α-bromoacetyl bromide (0.09 mL, 1.04 mmol) in methylene chloride (2 mL) under argon. The reaction mixture is allowed to warm to RT and stir for 2 h. The mixture is diluted with methylene chloride (40 mL) and wash successively with 10% citric acid (1 x 50 mL) and saturated sodium bicarbonate (1 x 50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting residue is dissolved in DMF (3 mL) and added via an addition funnel to a slurry of sodium hydride (25 mg, 1.04 mmol) in DMF (2 mL) which is cooled to 0°C. After 2 h of stirring, the mixture is poured over an ice cooled solution of 10% citric acid (50 mL) and extracted with ethyl acetate (3 x 40 mL). The combined extracts are washed with saturated sodium bicarbonate (1 x 50 mL), dried (Na_2SO_4), filtered, concentrated, and chromatographed on silica gel to afford the title compound.

c) Ethyl-3-[3,4-dihyro-8-iodo-2-thione-5-oxo-1H-1,4-benzodiazepine]-4-propanoate

To a solution of ethyl-3-[3,4-dihyro-8-iodo-2,5-dioxo-1H-1,4-benzodiazepine]-4-propanoate (1.0 g, 2.49 mmol) in THF (10 mL) at RT and under an atmosphere of nitrogen is added Lawesson's reagent (1.0 g), and the reaction is heated at 50°C for 2 h. The reaction mixture is allowed to cool to RT and is concentrated in vacuo. Silica gel chromatography (gradient 40-60% EtOAc/hexanes) gives the title compound.

d) Ethyl-3-[4H-imidazo[1,2-a][1,4]benzodiazepine-5(6H)-1-methyl-6-oxo-9-iodo]-4-propanoate

To a vigorously stirred biphasic solution of ethyl-3-[3,4-dihyro-8-iodo-2-thione-5-oxo-1H-1,4-benzodiazepine]-4-propanoate (0.95 g, 2.27 mmol), methyl iodide (0.2 g) and a catalytic amount of tetrabutylammonium hydrogen sulfate in CH_2Cl_2 (10 mL) and water (10 mL) is added 2 N NaOH (1.2 mL) at RT. After 2 h, the layers are separated and the aqueous layer is washed with CH_2Cl_2 (2 x 25 mL). The combined organic extracts are dried (Na_2SO_4), filtered and concentrated in vacuo. The resulting residue is dissolved in toluene (10 mL) and treated with

propargyl amine (0.64 mL, 4-fold excess) and pyridine hydrogen chloride (0.23 g, 1 mol eq). The reaction is heated to reflux for 6 h, then was allowed to cool to RT. Concentration and silica gel chromatography (EtOAc) gives the title compound.

e) Ethyl-3-[4H-imidazo[1,2-a][1,4]benzodiazepine-5(6H)-1-methyl-6-oxo-9-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]]-4-propanoate

A mixture of ethyl-3-[4H-imidazo[1,2-a][1,4]benzodiazepine-5(6H)-1-methyl-6-oxo-9-iodo]-4-propanoate(2 mmol), 2-(methylaminomethyl)benzimidazole (3 mmol), DIEA (1.8 mL, 10 mmol), and $(Ph_3P)_2PdCl_2$ (140 mg, 0.2 mmol) in N-methyl-2-pyrrolidinone (20 mL) is heated to 110°C under a CO balloon for 3 h. The mixture is then concentrated and the residue is purified by silica gel flash chromatography to give the title compound.

f) 3-[4H-Imidazo[1,2-a][1,4]benzodiazepine-5(6H)-1-methyl-6-oxo-9-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]]-4-propanoic acid

A solution of ethyl-3-[4H-imidazo[1,2-a][1,4]benzodiazepine-5(6H)-1-methyl-6-oxo-9-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]]-4-propanoate (54 mmol), $LiOH \cdot H_2O$ (0.79 mmol), THF (5 mL), and water (2 mL) is stirred at RT overnight. The mixture is concentrated, the residue is dissolved in water, and the resulting solution is neutralized with 3 N HCl. The precipitate is collected and dried in vacuo to afford the title compound.

Example 63

Preparation of 4-[4-[2-(1H-benzimidazol-2-yl)ethyl]-1-piperazinyl]-1-piperidineacetic acid

a) Ethyl 4-[4-[(tert-butoxycarbonyl)]-1-piperazinyl]-1-piperidineacetate

The title compound is prepared from tert-butyl 1-piperazinecarboxylate (Aldrich) and ethyl 4-oxo-1-piperidineacetate (Porter et al. EPA 0 542 363 A2) by $NaCNBH_3$ reductive amination according to the method of Porter et al., EPA 0 542 363 A2.

b) Ethyl 4-(1-piperazinyl)-1-piperidineacetate

A solution of ethyl 4-[4-[(tert-butoxycarbonyl)]-1-piperazinyl]-1-piperidineacetate and 4 M HCl/dioxane in CH_2Cl_2 is stirred at RT for 18 h. The reaction mixture is concentrated to give the title compound as the hydrochloride salt.

c) 2-[2-Chloroethyl)]benzimidazole

A solution of 2-benzimidazoleethanol and thionyl chloride in CH_2Cl_2 is heated at reflux for 2 h. The mixture is evaporated to give the title compound.

d) Ethyl of 4-[4-[2-(1H-benzimidazol-2-yl)ethyl]-1-piperazinyl]-1-piperidineacetate

A solution of ethyl 4-(1-piperazinyl)-1-piperidineacetate, 2-[2-chloroethyl)]benzimidazole, and DIEA in DMF is stirred at RT for 18 h. The mixture is concentrated and purified by chromatography to give the title compound.

e) 4-[4-[2-(1H-Benzimidazol-2-yl)ethyl]-1-piperazinyl]-1-piperidineacetic acid

A solution of ethyl of 4-[4-[2-(1H-benzimidazol-2-yl)ethyl]-1-piperazinyl]-1-piperidineacetate and 1.0 N NaOH in MeOH is stirred at RT. After 18 h, the mixture is neutralized with AcOH, desalted through an XAD-2 column, and lyophilized to give the title compound.

Example 64

Preparation of 1-hydroxy-4-[4-[3-(1H-benzimidazol-2-yl)propyl]-1-piperazinyl]-cyclohexaneacetic acid

a) tert-Butyl 1-hydroxy-4-[4-[2-(1H-benzimidazol-2-yl)propyl]-1-piperazinyl]-cyclohexaneacetate

A solution of tert-butyl 1-hydroxy-4-(1-piperazinyl)-cyclohexaneacetate (EPA 0 537 980 A1), 2-(3-bromopropyl)benzimidazole (*J. Org. Chem.* **1962**, *27*, 2165), and DIEA in DMF is stirred at RT for 18 h. The mixture is concentrated and purified by chromatography to give the title compound.

b) 1-Hydroxy-4-[4-[2-(1H-benzimidazol-2-yl)propyl]-1-piperazinyl]-cyclohexaneacetic acid

A solution of tert-butyl 1-hydroxy-4-[4-[2-(1H-benzimidazol-2-yl)propyl]-1-piperazinyl]-cyclohexaneacetate and 4 M HCl/dioxane in CH_2Cl_2 is stirred at RT. After 18 h, the mixture is evaporated to give the title compound.

Example 65

Preparation of N-[3-[1-[[2-(2-Benzimidazolyl)ethyl]carbonyl]piperidinyl]carbonyl]-β-alanine

Following the procedures of Beavers et. al., WO 95/25091, Example 1, except substituting (2-benzimidazolyl)propionic acid for N^{α}-Boc-D-lys(Cbz)-OH, gives the title compound.

Example 66

Preparation of 2-[(Benzimidazol-2-yl)methyl]- 5-[2-(carboxy-ethyl)amino]carbonyl] -2,3-dihydro-3-oxo-1H-isoindole

Following the procedures of Preparation 1-12 in Hartman, et al., EP 0 540 334 A1, for the preparation of 1-H-isoindole-5-carboxamide, 2,3-dihydro-N-(2-carboxy-ethyl)-2-[2-(piperidinyl)ethyl]-3-oxo, except substituting 2-(aminomethyl)benzimidazole (Aldrich) for Boc-4-piperidine-2-ethylamine, the title compound is prepared.

Example 67

Preparation of [3(R)-[2-(benzimidazol-2-yl)ethyl]-2-oxopiperidinyl]acetyl-3(R)-methyl -β-alanine

a) Methyl 4-(benzimidazol-2-yl) butanoate

Following the procedure of Example 36(a), except substituting 1,2-diaminobenzene for the 2,3-diaminopyridine, the title compound is prepared.

b) 4-(Benzimidazol-2-yl) butanoic acid

Following the procedure of Example 36(b), methyl 4-(benzimidazol-2-yl) butanoate is saponified to afford the title compoud.

c) [3(R)-[2-(Benzimidazol-2-yl)ethyl]-2-oxopiperidinyl]acetyl-3(R)-methyl -β-alanine

Following the procedure of Duggan et al (*J. Med. Chem.* **1995**, *38*, 3332), except using 4-(benzimidazol-2-yl) butanoic acid instead of (N-Boc-piperidin-4-yl)butanoic acid, the title compound is prepared.

Example 68

Preparation of 4-[[[[2-(benzimidazolyl)methyl]carbonyl]methylamino]-acetyl]phenoxyacetic acida) 4-[2-(Boc-methylamino)acetyl]phenol

A solution of di-tert-butyl dicarbonate (5.96 g, 27.3 mmol) in 1,4-dioxane (25 mL) was added dropwise at 0°C to a mixture of 4-[2-(methylamino)acetyl]phenol hydrochloride (5.0 g, 24.8 mmol), 1,4-dioxane (30 mL), H_2O (25 mL) and 1.0 N NaOH (25 mL, 25 mmol). After 24 h, the reaction was warmed to RT and stirred for 1.5 h. More 1.0 N NaOH (25 mL, 25 mmol) was added, and the reaction was stirred for an additional 0.5 h at RT, and concentrated. The residue was diluted with EtOAc (80 mL), and the mixture was acidified to pH 2 using 1.0 M $NaHSO_4$. The resulting mixture was extracted with EtOAc, and the combined organic layers were washed with H_2O and dried (Na_2SO_4). Filtration and concentration gave the title compound (6.49 g, 99%): ^1H NMR (250 MHz, $CDCl_3$) δ 6.70-8.05 (m, 4 H), 4.53 (s, 2H), 2.98 (s, 3H), 1.50 (s, 9H).

b) Benzyl 4-[2-(Boc-methylamino)acetyl]phenoxyacetate

A mixture of the compound of Example 68(a) (5.04 g, 19.0 mmol) and K_2CO_3 (2.63 g, 19.0 mmol) in acetone (100 mL) was stirred at reflux under argon for 1h. The mixture was cooled to RT and benzyl bromoacetate (5.23 g, 22.8 mmol) was added. The reaction was heated at reflux for 18 h, then was cooled and filtered. The filter cake was washed with acetone, and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2 (300 mL) and washed sequentially with H_2O (50 mL) and brine (50 mL). Drying (Na_2SO_4), concentration, and flash chromatography (silica gel, 1:3 EtOAc/hexanes) yielded the title compound (7.28 g, 93%): ^1H NMR (250 MHz, $CDCl_3$) δ 6.85-7.95 (m, 9 H), 5.23 (s, 2H), 4.71 (s, 2H), 4.55 (d, 2H), 2.95 (d, 3H), 1.45 (d, 9H).

c) Benzyl 4-[2-(methylamino)acetyl]phenoxyacetate hydrochloride

A mixture of the compound of Example 68(b) (7.26 g, 17.57 mmol) and 4 M HCl in 1,4-dioxane (150 mL) was stirred for 1 h at RT. Concentration and trituration with Et_2O afforded the title compound as a white powder (5.93 g, 97%):

^{1}H NMR (250 MHz, CD_3OD) δ 7.05-8.00 (m, 9 H), 5.23 (s, 2H), 4.88 (s, 2H), 4.65 (s, 2H), 2.80 (s, 3H).

d) Benzyl 4-[[[[2-(benzimidazolyl)methyl]carbonyl]methylamino]acetyl]phenoxyacetate

A mixture of the compound of Example 68(c)(1 mmol), 2-(benzimidazolyl)acetic acid (1 mmol), EDC (1.5 mmol), and DIEA (3 mmol) in DMF (25 mL) is stirred at RT. The mixture is poured in to 5% $NaHCO_3$ and extracted with EtOAc. The organic phase is washed with H_2O, dried ($MgSO_4$) and concentrated. The residue is chromatographed (silica gel) to give the title compound.

e) 4-[[[[2-(Benzimidazolyl)methyl]carbonyl]methylamino]acetyl]phenoxyacetate

The compound of Example 68(d)(1 mmol) and 1N NaOH (1.5 mL) in CH_3OH (20 mL) is stirred and concentrated. The residue is dissolved in H_2O, extracted with CH_2Cl_2, and the aqueous phase is adjusted to pH 5 with dilute HCl to give the title compound.

Example 69

Preparation of 4-[[[[2-(Benzimidazolyl)methyl]carbonyl]methylamino]acetyl]-1,2-phenylenedioxydiacetic acid

a) 4-[2-(Boc-methylamino)acetyl]-1,2-dihydroxybenzene

Following the procedure of Example 68(a), except substituting adrenalone hydrochloride (5.0 g, 23.0 mmol) for 4-[2-(methylamino)acetyl]phenol hydrochloride, the title compound (1.2 g, 19%) was prepared following flash chromatography (silica gel, 1:1 EtOAc/hexanes): MS (ES) m/e 282.2 $[M+H]^+$.

b) Dimethyl 4-[2-(Boc-methylamino)acetyl]-1,2-phenylenedioxydiacetate

Following the procedure of Example 68(b), except substituting the compound of Example 69(a) (0.9 g, 3.2 mmol) for the compound of Example 68(a) and methyl bromoacetate (1.23 g, 8.0 mmol) for benzyl bromoacetate, the title compound (1.11 g, 81%) was prepared: MS (ES) m/e 426.2 $[M+H]^+$.

c) Dimethyl 4-[2-(methylamino)acetyl]-1,2-phenylenedioxydiacetate hydrochloride

Following the procedure of Example 68(c), except substituting the compound of Example 69(b) (1.11 g, 2.6 mmol) for the compound of Example 68(b), the title compound was prepared (1.1 g, quantitative): MS (ES) m/e 326.0 $[M+H]^+$.

d) Dimethyl 4-[[[[2-(benzimidazolyl)methyl]carbonyl]methylamino]acetyl]-1,2-phenylenedioxydiacetate

Following the procedure of procedure of Example 68(d), except substituting the compound of Example 69(c) for the compound of Example 68(c), gives the title compound.

e) 4-[[[[2-(Benzimidazolyl)methyl]carbonyl]methylamino]acetyl]-1,2-phenylenedioxydiacetic acid

Following the procedure of procedure of Example 68(e), except substituting the compound of Example 69(d) for the compound of Example68(d), gives the title compound.

Example 70

Preparation of N-[3-[[[(2-Benzimidazolyl)methyl]carbonyl]amino]benzoyl]-β-alanine

a) Benzyl N-[3-[[[(2-benzimidazolyl)methyl]carbonyl]amino]benzoyl]-β-alaninate

A mixture of benzyl N-(3-aminobenzoyl)-β-alaninate (Alig, et. al., EPA 372486)(1 mmol), (2-benzimidazolyl)acetic acid (1 mmol), EDC (1.5 mmol), and DIEA (3 mmol) in DMF (25 mL) is stirred at RT. The mixture is poured into 5% $NaHCO_3$ and extracted with EtOAc. The combined organic phase is washed with H_2O, dried ($MgSO_4$) and concentrated. The residue is chromatographed (silica gel) to give the title compound.

b) N-[3-[[[(2-Benzimidazolyl)methyl]carbonyl]amino]benzoyl]-β-alanine

A mixture of the compound of Example 70(a)(1 mmol) and 1N NaOH (1.5 mL) in CH_3OH (20 mL) is stirred and concentrated. The residue is dissolved in H_2O, extracted with CH_2Cl_2, and the aqueous phase is adjusted to pH 5 with dilute HCl to give the title compound.

Example 71

Preparation of [[1-[N-[[(2-Benzimidazolyl)methyl]carbonyl]tyrosyl]-4-piperidinyl]oxy]acetic acid

a) tert-Butyl [[1-[N-[[(2-benzimidazolyl)methyl]carbonyl]tyrosyl]-4-piperidinyl]oxy]acetate

A mixture of tert-butyl [(1-tyrosyl-4-piperidinyl)oxy]acetate (Alig, et. al., EPA 372486)(1 mmol), (2-benzimidazolyl)acetic acid (1 mmol), EDC (1.5 mmol), and DIEA (3 mmol) in DMF (25 mL) is stirred at RT. The mixture is poured into 5% $NaHCO_3$ and extracted with EtOAc. The combined organic phase is washed with H_2O, dried ($MgSO_4$) and concentrated. The residue is chromatographed (silica gel) to give the title compound.

b) [[1-[N-[[(2-Benzimidazolyl)methyl]carbonyl]tyrosyl]-4-piperidinyl]oxy]acetic acid

A mixture of the compound of Example 71(a)(1 mmol) and CF_3CO_2H in CH_2Cl_2 is stirred and concentrated to give the title compound.

Example 72

Preparation of (S)-4-[[[(2-Benzimidazolyl)methyl]carbonyl]glycyl]-3-methoxycarbonylmethyl-2-oxopiperazine-1-acetic acid

Following the procedure of Sugihara, et. al., EP 0529858, Example 59, except substituting (2-benzimidazolyl)acetic acid for 4-amidinobenzoic acid hydrochloride, gives the title compound.

Example 73

Preparation of (3S,5S)-5-[[4-[(2-Benzimidazolyl)methyl]phenyl]oxymethyl]-3-carboxymethyl-2-pyrrolidinone

a) 4-[(2-Benzimidazolyl)methyl]phenol

Following the general procedure of Wahlgren and Addison, J. Heterocycl. Chem., **1989**, *26*, 541-543, except substituting 4-(hydroxy)phenylacetic acid for 2-(hydroxy)phenylacetic acid, gives the title compound.

b) (3S,5S)-5-[[4-[(2-Benzimidazolyl)methyl]phenyl]oxymethyl]-3-[(tert-butoxycarbonyl)methyl]-2-pyrrolidinone

Following the procedure of Himmelsbach, et.al., Australian Patent Application AU-A-86926/91, Example 51, substituting the compound of Example 73(a) for 4'-cyano-3'-fluoro-4-hydroxy)biphenyl, gives the title compound.

c) (3S,5S)-5-[[4-[(2-Benzimidazolyl)methyl]phenyl]oxymethyl]-3-carboxymethyl-2-pyrrolidinone

The compound of Example 73(b) is treated with CF_3CO_2H in CH_2Cl_2 to give the title compound.

Example 74

Preparation of 1-[(2-Benzimidazolyl)methyl]-3-[4-(2-carboxyethyl)phenyl]-4-methoxy-3-pyrrolin-2-one

Following the procedures of Linz, et. al., EP 0567968, except substituting (2-benzimidazolyl)methanamine for 4-cyanoaniline, gives the title compound.

Example 75

Preparation of 2-[6-(benzimidazol-2-yl) methylaminocarbonyl)-1,2,3,4-tetrahydroisoquinolinyl]acetic acid

a) 6-Methoxy-1,2,3,4-tetrahydroisoquinoline

6-Methoxy-1,2,3,4-tetrahydroisoquinoline is prepared according to the method of D. J. Sall and G. L. Grunewald (J. Med. Chem. *1987*, 30, 2208-2216).

b) Ethyl 2-[6-Methoxy-1,2,3,4-tetrahydroisoquinolinyl]acetate

A solution of the compound of Example 75(a) (1.1 mmol), ethyl chloroacetate (1.17 mmol), and potassium carbonate (1.17 mmol) in acetonitrile (10 mL) is stirred for 18 hr. The mixture is then partitioned in a mixture of EtOAc and H_2O. The organic phase is rotary evaporated to an oil, which is purified by silica gel chromatography to afford the title compound.

c) Ethyl 2-[6-Hydroxy-1,2,3,4-tetrahydroisoquinolinyl]acetate

A solution of the compound of Example 75(b) (0.249 g, 1.0 mmol) and boron tribromide (1M in CH_2Cl_2 , 1.0 mL, 1.0mmol, mL) is stirred at -70 °C for 2 hr and then stirred at RT for 12 hr. The solution is rotary evaporated to an oil. The residue is taken up in EtOAc. EtOAc is washed with water (1X), 5% $NaHCO_3$(2X), water (1X). EtOAc is dried over Mg_2SO_4, filtered and rotary evaporated to afford the title compound.

d) Ethyl 2-[6-trifluoromethylsulfonyloxy-1,2,3,4-tetrahydroisoquinolinyl]acetate

A solution of the compound of Example 75(c) (0.235 g, 1.0 mmol) , trifluorosulfonic acid anyhdride (0.23 mL, 1.1mmol,) and Et_3N (0.32 mL, 1.5 mmol) in CH_2Cl_2 (5 mL)is stirred for 8 hr The solution is rotary evaporated to an oil. The residue is taken up in EtOAc. EtOAc is washed with 5% $NaHCO_3$ (2X), water (1X). EtOAc is dried over Na_2SO_4 , filtered and rotary evaporated to afford the title compound.

e) Ethyl 2-[6-carboxy-1,2,3,4-tetrahydroisoquinolinyl]acetate

A solution of the compound of Example 75(d) (0.367 g, 1.0mmol), palladium(II)bis-acetate (0.022 g, 0.1mmol,), triphenylphosphine (0.262 g, 1.0mmol), diisopropylamine (0.34 mL, 2.5 mmol), NMP (5 mL), in aqueous ammonium carbonate (10%) is stirred for 8 hr under an atmosphere of carbon monoxide. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

f) Ethyl -[6-(benzimidazol-2-yl)methylaminocarbonyl)-1,2,3,4-tetrahydroisoquinolinyl]acetic acid

A solution of the compound of Example 75(e) (0.263 g, 1.0 mmol), the compound of (2-benzimidazolyl)acetic acid (0.34g, 1.0 mmol), EDC (0.191g, 1.0 mmol), HOBt (0.151 g, 1.0 mmol) and triethylamine (0.235 mL, 2.0 mmol) in DMF(7 mL) is stirred for 8 hr. The solution is rotary evaporated to an oil. The residue is purified by silica gel column to afford the title compound.

g) 2-[6-(benzimidazol-2-yl)methylaminocarbonyl)-1,2,3,4-tetrahydroisoquinolinyl]acetic acid

A solution of the compound of Example 75(f) (0.42 g, 1.0 mmol) in aqueous 1 N sodium hydroxide (1.5 mL, 1.5 mmol) and ethanol (5 mL) is stirred for 8 hr. The solution is rotary evaporated to an oil. The residue is purified by silica gel column to afford the title compound.

Example 76

Preparation of 2-[6-(benzimidazol-2-yl)methylaminocarbonyl)-1-oxo-1,2,3,4-tetrahydroisoquinolinyl]acetic acid

a) 6-Methoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline

6-Methoxy-1-oxo-1,2,3,4-tetrahydroisoquinoline is prepared according to the method of D. J. Sall and G. L. Grunewald, J. Med. Chem. (1987), *30*, 2208-2216.

b) Ethyl 2-[6-Methoxy-1-oxo-1,2,3,4-tetrahydroisoquinolinyl]acetate

A mixture of the compound of Example 76(a) (0.39 mmol) and NaH (0.17 g, 0.43 mmol, 60% oil dispersion) in THF (5 mL) is heated to reflux for 1 hr and then allowed to cool to room temperature. Ethyl chloroacetate (0.43 mmol) is added to the mixture, and the mixture is allowed to stir for 1 hr. The mixture is quenched with water (10 mL) and washed with EtOAc (2X 15 mL). The organic layers are combined, washed with water (10 mL) and rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

c) Ethyl 2-[6-Hydroxy-1-oxo-1,2,3,4-tetrahydroisoquinolinyl]acetate

A solution of the compound of Example 76(b) (0.263 g, 1.0 mmol) and boron tribromide (1M solution in CH_2Cl_2, 1.1 mL) is stirred at -70 °C for 2 hr and then at RT for 4 hr. The solution is rotary evaporated to an oil. The residueis taken up in EtOAc. EtOAc is washed with water (1X), 5% $NaHCO_3$ (2X), water (1X).

EtOAc is dried over $MgSO_4$, filtered and rotary evaporated to afford the title compound.

d) Ethyl 2-[6-trifluoromethylsulfonyloxy-1-oxo-1,2,3,4-tetrahydroisoquinolinyl]acetate

A solution of the compound of Example 76(c) (3.4 mmol) and trifluorosulfonic acid anyhdride (3.4 mmol, mL) in pyridine (5 mL) is chilled at 0° and allowed to warm to room temperature for 1 hr. The mixture is quenched with water (5 mL) and washed with EtOAc (2X 7 mL). The organic layers are combined, washed with water (7 mL) and rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

e) Ethyl 2-[6-carboxy-1-oxo-1,2,3,4-tetrahydroisoquinolinyl]acetate

A solution of the compound of Example 76(d) (0.23 g, 1.0 mmol), palladium(II)bis-acetate (0.026 g, 0.1 mmol), triphenylphosphine (0.262 g, 1.0 mmol), diisopropylamine (0.23 mL, 2.0 mmol), NMP (7 mL), in aqueous ammonium carbonate "(10 %) is stirred for 8 hr under an atmosphere of carbon monoxide. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

f) Ethyl -[6-(benzimidazol-2-yl)methylaminocarbonyl)-1,2,3,4-tetrahydroisoquinolinyl]acetic acid

A solution of the compound of Example 76(e) (0.34 g, 1.0 mmol), the compound of (2-benzimidazolyl)acetic acid (0.43 g, 1.0 mmol), EDC (0.191 g, 1.0 mmol), HOBt (0.15 g, 1.0 mmol) and triethylamine (0.234 mL, 2.3 mmol) in DMF(8 mL) is stirred for 8 hr. The solution is concentratred. The residue is purified by silica gel chromatography to afford the title compound.

Alternatively, a solution of the compound of Example 76(d) (0.23 g, 1.0 mmol), palladium(II)bis-acetate (0.026 g, 0.1 mmol), triphenylphosphine (0.262 g, 1.0 mmol), diisopropylamine (0.25 mL, 2.1 mmol), NMP (7 mL), and the compound

of Intermediate A (0.31 g, 1.0 mmol) in aqueous ammonium carbonate (10%) is stirred for 8 hr under an atmosphere of carbon monoxide. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

g) 2-[6-((benzimidazol-2-yl)methylaminocarbonyl)-1,2,3,4-tetrahydroisoquinolinyl]acetic acid

A The solution of the compound of Example 76(f) (0.25 g, 1.0 mmol) in aqueous 1 N sodium hydroxide (1.5 mL, 1.5 mmol) and ethanol (8 mL) is stirred for 8 hr. Solution is rotary evaporated to an oil. The residue is purified by silica gel to afford the title compound.

Example 77

Preparation of 2-[6-((benzimidazol-2-yl)methylcarbonylamino)tetralin]acetic acid

a) tert-butyl-5-amino-tetraline-2-acetate

Tert-butyl-5-amino-tetraline-2-acetate is prepared according to the methods described in M. J. Fisher, *et al.* (Scheme 12 and Example 28, parts A-D, EO 0635492, Jan. 25, 1995).

b) 2-[6-((benzimidazol-2-yl)methylcarbonylamino)tetralin]acetate

A solution of the compound of Example 77 (a) (0.261 g, 1.0 mmol), 2-(aminomethyl)benzimidazole (0.256g, 1.0 mmol), EDC (0.191g, 1.0 mmol) 1-hydroxybenzotriazole hydrate (0.152 g, 1.0 mmol), and triethylamine (0.234 mL, 2.1 mmol) in DMF (5 mL) is allowed to stir for 8 hr. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

A solution of the crude ester amide (0.32 g, 1.0 mmol) and trifluoroacetic acid (5 mL) in methylene chloride (5 mL) is allowed to stir for 1 hr. The solution is

rotary evaporated to an oil. The residue is treated with Et_2O. Filtration and drying *in vacuo* afforded the title compound.

Example 78

Preparation of 2-[6-((benzimidazol-2-yl)methylaminocarbonyl)tetralin]acetic acid

a) Ethyl-5-hydroxy-tetraline-2-acetate

The compound Ethyl-5-hydroxy-tetraline-2-acetic acid is prepared according to the method of M. J. Fisher *et al.* (EP 0635492, Scheme 6 and Example 20, parts A-D, p. 71).

b) Ethyl-5-trifluoromethylsulfonyloxy-tetraline-2-acetate

A solution of the compound of Example 78(b) (0.321g, 1.0 mmol) in CH_2Cl_2 (10 mL) is cooled to O° C.Trifluoromethylsulfonic acid anhydride (0.125 mL, 1.1 mmol) is added. The solution is stirred for 2 hr. The solution is rotary evaporated to an oil. The residue is taken up in EtOAc. EtOAc is washed with water (1X), 5% $NaHCO_3$, water (1X). EtOAc is dried over $MgSO_4$, filtered. Filtrate is rotary evaporated to afford the title compound.

c) Ethyl 6-carboxy-tetraline-2-acetate.

A solution of the compound of Example 78(c) (0.26 g, 1.0 mmol), palladium(II)bis-acetate (0.023g, 0.1 mmol), triphenylphosphine (0.262g, 1.0 mmol), diisopropylamine (0.245 mL, 2.1 mmol), NMP (10 mL), in aqueous ammonium carbonate (10%) is stirred for 8 hr under an atmosphere of carbon monoxide. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

d) Ethyl -[6-((benzimidazol-2-yl)methylaminocarbonyl)-tetraline-1-acetate

A solution of the compound of Example 78(c) (0.34 g, 1.0 mmol), the compound of (2-benzimidazolyl)acetic acid (0.32g, 1.0 mmol), EDC (0.191 g, 1.0

mmol), HOBt (0.152 g, 1.0 mmol) and triethylamine (0.23 mL, 2.1 mmol) in DMF(6 mL) is stirred for 8 hr. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

Alternatively, a solution of the compound of Example 78(b) (0.34 g, 1.0 mmol), palladium(II)bis-acetate (0.023g, 0.1 mmol), triphenylphosphine (0.262g, 1.0 mmol), diisopropylamine (0.23 mL, 2.1 mmol), NMP (10 mL), and the compound of Intermediate A (0.32 g, 1.0 mmol), in aqueous ammonium carbonate (10%) is stirred for 8 hr under an atmosphere of carbon monoxide. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

e) 2-[6-((benzimidazol-2-yl)methylaminocarbonyl)-tetraline-2-acetic acid.

A solution of the compound of Example 78(d) (0.31 g, 1.0 mmol) in aqueous 1 N sodium hydroxide (1.5 mL, 1.5 mmol) and ethanol (5 mL) is stirred for 8 hr. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

Example 79

Preparation of 2-[5-((benzimidazol-2-yl)methylcarbonylamino)-benzofuranl-propionic acid

a) Ethyl 1-carboxymethyloxy-4-nitrosalicylaldehyde

A solution of 1-hydroxy-4-nitrosalicylaldehyde (Aldrich) (0.167 g, 1.0 mmol), ethyl bromoacetate (0.166 g, 1.0mmol) potassium carbonate (0.276 g, 2.0mmol) and sodium iodide (0.015 g, 0.1 mmol) in THF (10mL) is heated to 80 °C for 24 hr. The solution is rotary evaporated to an oil and the residue is purified by silica gel chromatography to afford the title compound.

b) Ethyl 2-carboxy-5-nitrobenzofuran

A solution of the compound of Example 79(a) (0.229 g, 1.0 mmol), DBU (0.152 g, 1.0 mmol) in ethyl alcohol (10 mL) is allowed to stir at RT for 18 hr. The solution is rotary evaporated to an oil and the residue is treated with EtOH (10 mL). The solution is bubbled with HCl.gas for 2 minutes and refluxed for 5 hr. The solution is rotary evaporated to an oil. EtOAc is added and washed with water (2X), 5% citric acid (2X), water (1X), 5% $NaHCO_3$.(2X) and water (1X). EtOAc is rotary evaporated to afford the title compound.

c) Ethyl 2-(2-carboxy)ethylene-5-nitrobenzofuran

A cold solution (-78 °C) of the compound of Example 79(b) (0.235 g, 1.0 mmol)in THF (5 mL) is treated with DiBAL (1.0 M in THF, 1.0 mL, 1.0 mmol). The solution is stirred at -78 °C for 30 minutes and RT for 3 hr. The solution is treated with CH_3COOH (3 mL) followed by water (2 mL). The solution is rotary evaporated to an oil and treated with toluene to azeotrope off the acetic acid. Drying *in vacuo* afforded the crude aldehyde.

A solution of the phosphonate ester (0.224 g, 1.0 mmol),in THF (5 mL) is treated with sodium hydride (60% suspension in mineral oil, 0.04 g, 1.0 mmol)at 0° C for 1 hr. To the solution is added the aldehyde (0.235 g, 1.0 mmol). The solution is stirred at RT for 18 hr. The solution is rotary evaporated to an oil and the residue is purified by silica gel chromatography to afford the title compound.

d) tert-butyl 2-[5-amino-benzofuranyl]propionate

A solution of the compound of Example 79(c) (0.261 g, 1.0 mmol) in ethanol (5 mL) containing 10% palladium-on-carbon(0.026 g, 10% wt) is hydrogenated at 45 psi for 1 hr. The solution is filtered through Celite and the filtrate is rotary evaporated to an oil. Silica gel chromatography affords the title compound.

e) 2-[5-((benzimidazol-2-yl)methylcarbonylamino)-benzofuran]-propionic acid

A solution of the compound of Example 79(d) (0.263 g, 1.0 mmol), EDC (0.191 g, 1.0 mmol), 1-hydroxybenzotriazole (0.150 g, 1.0 mmol), the compound of 2-(aminomethyl)benzimidazole (0.234 g, 1.0 mmol) and triethylamine (0.288 mL, 2.0 mmol) in DMF (5.0 mL) is allowed to stir for 18 hr. The solution is rotary evaporated to an oil and the residue is purified by silica gel chromatography to afford the title compound.

A solution of the crude ester (0.263 g, 1.0 mmol) in MeOH (3.0 mL) is treated with 1 N NaOH (1.5 mL, 1.5 mmol) and water (2 mL). The solution is stirred at RT for 18 hr. The solution is rotary evaporated to an oil and purified by reversed phase chromatography to afford the title compound.

Example 80

Preparation of 2-[5-((benzimidazol-2-yl)methylcarbonylamino)-2,3-dihydro-benzofuran]-propionic acid

a) Ethyl-2-[5-amino-2,3-dihydro-benzofuranyl]propionate

In the chromatographic purification of the compound of Example 79(d) the title compound is also obtained.

b) 2-[5-(6-aminopyridinyl-2-methylcarbonylamino)-benzofuran]-propionic acid

A solution of the compound of Example 80(a) (0.263 g, 1.0 mmol), EDC (0.191g, 1.0 mmol), 1-hydroxybenzotriazole (0.15g, 1.0 mmol), the compound of 2-(aminomethyl)benzimidazole (0.32 g, 1.0 mmol) and triethylamine (0.288 mL, 2.0 mmol) in DMF (5.0 mL) is allowed to stir for 18 hr. The solution is rotary evaporated to an oil and the residue is purified by silica gel chromatography to afford the title compound.

A solution of the crude ester (0.290g, 1.0 mmol) in MeOH (5.0 mL) is treated with 1N NaOH (1.2 mL, 1.2 mmol) for 18 hr. The solution is rotary

evaporated to an oil and purified by reversed-phase chromatography to afford the title compound.

Example 81

Preparation of 2-[5-(6-aminopyridinyl-2-methylaminocarbonyl)-benzofuran]-propionic acid

a) 2-Ethyloxycarbonyl-5-(tert-butyl-dimethylsilyloxy)-benzofuran

A solution of 2-Ethyloxycarbonyl-5-(hydroxy)-benzofuran is prepared via the procedure described in M. L. Denny, *et al.* (EP 0655439, 31,5,95) (0.206 g, 1.0 mmol), tert-butyl-dimethylsilylchloride (0.23 mL, 1.0 mmol) and imidazole (0.34 g, 1.0 mmol) in THF is allowed to stir for 4 hr. The solution is rotary evaporated to an oil. EtOAc is added and washed with water. EtOAc is rotary evaporated to afford the title compound.

b) 2-Hydrocarbonyl -5-(tert-butyl-dimethylsilyloxy)-benzofuran

A cold solution (-78 °C) of the compound of Example 81(a) (0.35 g, 1.0 mmol)in THF (5 mL) is treated with DiBAL (1.0 M in THF, 1.0 mL, 1.0 mmol). The solution is stirred at -78 °C for 30 minutes and RT for 3 hr. The solution is treated with CH_3COOH (3 mL) followed by water (2 mL). The solution is rotary evaporated to an oil and treated with toluene to azeotrope off the acetic acid. Drying *in vacuo* afforded the aldehyde.

c) Ethyl 2-[5-(tert-butyl-dimethylsilyloxy)-benzofuran]-acrylate

A solution of the phosphonate ester (0.224 g, 1.0 mmol),in THF (5 mL) is treated with sodium hydride (60% suspension in mineral oil, 0.04 g, 1.0 mmol)at 0° C for 1 hr. To the solution is added the above aldehyde(0.235 g, 1.0 mmol). The solution is stirred at RT for 18 hr. The solution is rotary evaporated to an oil and the residue is purified by silica gel chromatography to afford the title compound.

d) 2-Ethyl 2-[-5-(hydroxy)-benzofuran]-propionate

A mixture of the compound of Example 81(c) (0.234g, 1.2 mmol) and 10% palladium-on-carbon (0.023 g, 10% wt) in EtOH(5 mL).is hydrogenated at 50 psi for 1 hr. Filtration through Celite and concentration afforded.the ester (0.169 g, 56%).

A solution of the crude ester (0.34 g, 1.0 mmol) and tetraethylammonium fluoride (0.149 g, 1.0 mmol) in THF (10 mL) is allowed to stir at RT for 18 hr. The solution is rotary evaporated to an oil and purified by silica gel chromatography.

e) 2-Ethyl 2-[-5-(trifluoromethylsulfonyloxy)-benzofuran]-propionate

A solution of the compound of Example 81(d) (0.366 g, 1.0 mmol) and Et_3N(0.23 mL, 1.5 mmol) in CH_2Cl_2 (10 mL) at 0 °C is treated with trifluoromethylsulfonic acid anhydride (0.21 mL, 1.1 mmol). After 2 hr solution is rotary evaporated to an oil. The residue is taken up in EtOAc. EtOAc is washed successively with water(1X), 5% $NaHCO_3$ (2X), water (1X). EtOAc is dried over $MgSO_4$, and filtered. Filtrate is rotary evaporated to afford the title compound.

f) 2-Ethyl 2-[-5-(carboxy)-benzofuran]-propionate

A solution of the compound of Example 81(e) (0.366g, 1.0 mmol), palladium(II) bis-acetate (0.023g, 0.1 mmol), triphenylphospine (0.262g, 1.0 mmol), diisopropylethylamine (0.23 mL, 2.1 mmol), NMP (7 mL) in aqueous sodium bicarbonate (10%, 6 mL) is allowed to stir. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

g) 2-Ethyl 2-[-5-(6-(6-aminopyridinyl-2-methylaminocarbonyl)-benzofuran]-propionate

[redacted]

A solution of the compound of Example 81(f) (0.366 g, 1.0 mmol), the compound of (2-benzimidazolyl)acetic acid (0.23g, 1.0 mmol), EDC (0.191 g, 1.0mmol), HOBt (0.152g, 1.0mmol) and triethylamine (0.235 mL, 2.1mmol) in DMF(8 mL) is stirred for 8 hr. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

Alternatively, a solution of the compound of Example 81(e) (0.366g, 1.0mmol), palladium(II)bis-acetate (0.023g, 0.1 mmol), triphenylphosphine (0.262g, 1.0 mmol), diisopropylamine (0.23 mL, 2.1 mmol), NMP (10 mL), and the compound of Intermediate A (0.32g, 1.0 mmol) in aqueous ammonium carbonate (10%, 10 mL) is stirred for 8 hr under an atmosphere of carbon monoxide. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

h) 2-[-5-(6-(6-aminopyridinyl-2-methylaminocarbonyl)-benzofuran]-propionic acid

A solution of the compound of Example 81(g) (0.366g, 1.0 mmol) in aqueous 1 N sodium hydroxide (1.5 mL, 1.5 mmol) and ethanol (8 mL) is stirred for 8 hr. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

Example 82

Preparation of 2-[5-((benzimidazol-2-yl)methylaminocarbonyl)-2,3-dihydro-benzofuran]-propionic acid

a) 2-tert-Butyl 2-[-5-(hydroxy)-2,3-dihydro-benzofuran]-propionate

The chromatographic purification in Example 81(d) also provides the title compound.

b) 2-tert-Butyl 2-[-5-(trifluoromethylsulfonyloxy)-2,3-dihydro-benzofuran]-propionate

A cold solution of the compound of Example 82(a) (0.28 g, 1.0 mmol) and Et_3N (0.23 mL, 2.1 mmol) in CH_2Cl_2 (5 mL) is treated with trifluoromethylsulfonic acid anhydride (0.15 mL, 1.1 mmol) for 2 hr. The solution is rotary evaporated to an oil. The residue is taken up in EtOAc. EtOAc is washed with water (1X), 5% $NaHCO_3$ (2X), water (1X). EtOAc is dried over $MgSO_4$, filtered, and filtrate is rotary evaporated to afford the title compound.

c) 2-tert-Butyl 2-[-5-(carboxy)-2,3-dihydro-benzofuran]-propionate

A solution of the compound of Example 82(b) (0.24 g, 1.0 mmol), palladium(II) bis-acetate (0.023g, 0.1 mmol), triphenylphospine (0.262g, 1.0 mmol), diisopropylethylamine (0.23 mL, 2.1 mmol), NMP (8 mL) in aqueous sodium bicarbonate (10 mL, 10%) is allowed to stir at RT for 8 hr. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

d) 2-tert-Butyl 2-[-5-(6-(6-aminopyridinyl-2-methylaminocarbonyl)-2,3-dihydro-benzofuran]-propionate

A solution of the compound of Example 82(c) (0.366g, 1.0 mmol), the compound of (2-benzimidazolyl)acetic acid (0.23g, 1.0 mmol), EDC (0.191g, 1.0 mmol), HOBt (0.152g, 1.0 mmol) and triethylamine (0.23 mL, 2.1 mmol) in DMF(8 mL) is stirred for 8 hr. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

Alternatively, a solution of the compound of Example 82(b) (0.366g, 1.0 mmol), palladium(II)bis-acetate (0.023 g, 0.1 mmol), triphenylphosphine (0.262 g, 1.0 mmol), diisopropylamine (0.23 mL, 2.1 mmol), NMP (10 mL), and the compound of Intermediate A (0.23 g, 1.0 mmol), in aqueous ammonium carbonate (10%, 10 mL) is stirred for 8 hr under an atmosphere of carbon monoxide for 8 hr. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

e) 2-[-5-(6-((benzimidazol-2-yl)methylaminocarbonyl)-2,3-dihydro-benzofuran]-propionic acid

A solution of the compound of Example 82(d) (0.37 g, 1.0 mmol) in aqueous 1 N sodium hydroxide (1.5 mL, 1.5 mmol) and ethanol (8 mL) is stirred for 8 hr. The solution is rotary evaporated to an oil. The residue is purified by silica gel chromatography to afford the title compound.

Example 83

Preparation of 1-[(1H-benzimidazol-2-yl)methyl]-3-{4[(2-ethoxycarbonyl)ethyl)]phenyl}-3-oxo-imidazolidine

a) 2-Aminomethyl-1-p-toluenesulfonyl-benzimidazole

A solution of 2-Methylbenzimidazole (1 mmol), p-toluenesulfonyl chloride (1.05 mmol) and Et_3N (1.05 mmol) in water (2 mL) and THF (1 mL) is allowed to stir for 4 hr. The mixture is concentrated by rotary evaporation and diluted with water (10 mL). The solution is washed with EtOAc (2X 15 mL). The organic layers are combined, washed with water (5 mL) and rotary evaporated to an oil.

A solution of the aforementioned oil (2-Methyl-1-p-toluenesulfonyl-benzimidazole) (1 mmol) and N-bromosuccinimide (1.05 mmol) in CCl_4 (10 mL) is allowed to reflux for 18 hr. Upon cooling a white solid precipitates from solution. The solid is filtered, triturated with CCl_4 and dried *in vacuo* to a solid.

A solution of Boc_2NH (1 mmol) and potassium hydroxide (1 mmol) in ethanol (5 mL) is allowed to stir for 1 hr. Anhydrous ethyl ether (15 mL) is added and the mixture is filtered to afford the salt as a white solid. A solution of the aforementioned solid 2-bromomethyl-1-p-toluenesulfonylbenzimidazole (1 mmol) and $(Boc)2N^- K^+$ (mmol) in THF (10 mL) is to stir at 60° for 18 hr. The mixture is rotary evaporated to an oil.

A solution of the 2-[bis-(tert-butyloxycarbonyl)aminomethyl]-1-p-toluenesulfonylbenzimidazole (1 mmol) in TFA (1.1 mmol) and CH_2Cl_2 is allowed to stir for 1 hr. The solution is rotary evaporated to an oil, which is purified by chromatography to afford the title compound.

b) Ethyl 2-[4-(2-hydroxyethylamino)phenyl]propionate

This compound is prepared following the procedure of F. Himmelsbach *et al.* (Example V, p. 44, EP 0587134, Sept. 8, 1993), in which glycolaldehyde dimer (Aldrich) (mmol) is added to a solution of methyl 2-(4-aminophenyl)propionate 1 (1 mmol) in aqueous acetonitrile (pH 6-7) (mL), followed by sodiumcyanoborohydride (1.1 mmol), and the mixture is allowed to stir for 1 hr. The mixture is rotary evaporated to an oil, and the residue is dissolved in a mixture of ice water and ethyl acetate. The water layer is neutralized with 4 N sodium hydroxide and washed with ethyl acetate. The organic phase is rotary evaporated to an oil. A solution of the oil in ethyl acetate is purified on a silica gel column to give the title compound.

c) N-[(1-p-toluenesulfonyl-1H-benzimidazol-2-yl)methyl]-N'-hydroxyethyl-N'-{4[(2-ethoxycarbonyl)ethyl)]phenyl}-urea

This compound is prepared following the procedures of F. Himmelsbach *et al.* (EP 0587134, Sept. 8, 1993 and EP 0612741, Feb.21, 1994), in which a solution of the compound of Example 83(a) (1 mmol) and phosgene (1.1 mmol) in THF (20 mL) is allowed to stir at -20° for 20 minutes. The compound of Example 83(b) (1.0 mmol) is added to the solution and the resulting mixture is allowed to stir for 18 hr. The resulting solution is rotary evaporated. A solution of the residue in ethyl acetate is washed with 5% citric acid, followed by water. The organic phase is rotary evaporated to an oil. . A solution of the oil in ethyl acetate is purified on a silica gel column to give the title compound.

d) N^1-[(1-p-toluenesulfonyl-1H-benzimidazol-2-yl)methyl]-N^3-{4[(2-ethoxycarbonyl)ethyl)]phenyl}-2-oxo-imidazolidine

This compound is prepared following the procedures of F. Himmelsbach *et al.* (Example III, EP 0587134, Sept. 8, 1993 and EP 0612741, Feb.21, 1994), in which a solution of the compound of Example 83(c) (1 mmol), methanesulfonylchloride (1.2 mmol) and triethylamine (1.2 mmol) in methylene chloride (5 mL) is allowed to stir at 0° for 1 hour. The mixture is partitioned in a mixture of water and methylene chloride. The organic phases are combined and dried over anhydrous sodium sulfate and rotary evaporated.

A solution of the residue and sodium iodide (1.1 mmol) in acetone (5 mL) is heated to reflux for 3 hr and then rotary evaporated to an oil. Potassium-bis(trimethylsilyl)azide (1.2 mmol) is added to a solution of the residue in DMF (5 mL), cooled to 0°. The solution is allowed to warm to room temperature over 30

min. and the rotary evaporated to an oil. The residue is partitioned in a mixture of water and methylene chloride. The organic phases are combined and dried over anhydrous sodium sulfate and rotary evaporated. A solution of the oil in ethyl acetate is purified on a silica gel column to give the title compound.

e) N^1-[(1H-benzimidazol-2-yl)methyl]-N^3-{4[(2-carboxyl)ethyl)]phenyl}-2-oxo-imidazolidine

A solution of the compound of Example 83(d) (1 mmol) in THF (5 mL) and 1 N sodium hydroxide (1.2 mL, 1.2 mmol) is allowed to stir for 18 hr. The mixture is neutralized with conc. hydrochloric acid and purified on a silica gel column to give the title compound.

Example 84

Parenteral Dosage Unit Composition

A preparation which contains 20 mg of the compound of Example 1 as a sterile dry powder is prepared as follows: 20 mg of the compound is dissolved in 15 mL of distilled water. The solution is filtered under sterile conditions into a 25 mL multi-dose ampoule and lyophilized. The powder is reconstituted by addition of 20 mL of 5% dextrose in water (D5W) for intravenous or intramuscular injection. The dosage is thereby determined by the injection volume. Subsequent dilution may be made by addition of a metered volume of this dosage unit to another volume of D5W for injection, or a metered dose may be added to another mechanism for dispensing the drug, as in a bottle or bag for IV drip infusion or other injection-infusion system.

Example 85

Oral Dosage Unit Composition

A capsule for oral administration is prepared by mixing and milling 50 mg of the compound of Example 1 with 75 mg of lactose and 5 mg of magnesium stearate. The resulting powder is screened and filled into a hard gelatin capsule.

Example 86

Oral Dosage Unit Composition

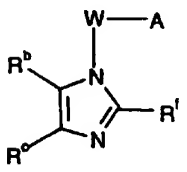
A tablet for oral administration is prepared by mixing and granulating 20 mg of sucrose, 150 mg of calcium sulfate dihydrate and 50 mg of the compound of

Example 1 with a 10% gelatin solution. The wet granules are screened, dried, mixed with 10 mg starch, 5 mg talc and 3 mg stearic acid; and compressed into a tablet.

The above description fully discloses how to make and use the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprises the state of the art and are incorporated herein by reference as though fully set forth.

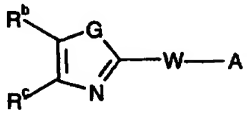
What is claimed is:

1. A compound according to formula (I) or (II) or (III) or (IV) or (V):



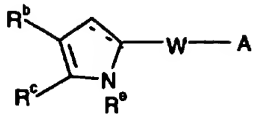
(I)

or



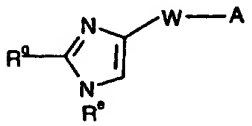
(II)

or



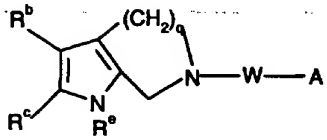
(III)

or



(IV)

or



(V)

wherein:

W is - $(CHR^g)_b$-V'- or phenyl;

A is a fibrinogen receptor antagonist template;

V' is $CONR^{21}$ or $NR^{21}CO$;

G is NR^e, S or O;

R^g is H, C_{1-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl or Ar- C_{0-6}alkyl;

R^{21} is Het-$(CH_2)_{0-6}$-U'-$(CH_2)_{1-6}$-, C_{3-7}cycloalkyl-$(CH_2)_{0-6}$-U'-$(CH_2)_{1-6}$-, or

Ar-$(CH_2)_{0-6}$-U'-$(CH_2)_{1-6}$-;

U' is $CONR^f$ or NR^fCO;

R^f is H, C_{1-6}alkyl or Ar-C_{1-6}alkyl;

R^e is H, C_{1-6}alkyl, Ar-C_{1-6}alkyl, Het-C_{1-6}alkyl, C_{3-7}cycloalkyl-C_{1-6}alkyl, $(CH_2)_qOH$ or $(CH_2)_kCO_2R^g$;

k is 0, 1 or 2;

q is 1 or 2;

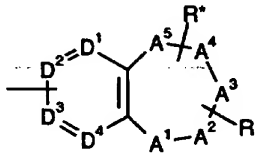
b is 0, 1 or 2;

R^b and R^c are independently selected from H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, or C_{3-6}cycloalkyl-C_{0-6}alkyl, halogen, CF_3, OR^f, $S(O)_kR^f$, COR^f, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, or R^b and R^c are joined together to

form a five or six membered aromatic or non-aromatic carbocyclic or heterocyclic ring, optionally substituted by up to three substituents chosen from halogen, CF_3, C_{1-4}alkyl, OR^f, $S(O)_kR^f$, COR^f, CO_2R^f OH, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, and $CH_2N(R^f)_2$, or methylenedioxy;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein the fibrinogen receptor antagonist template A is



wherein:

A^1 to A^5 form an accessible substituted seven-membered ring, which may be saturated or unsaturated, optionally containing up to two heteroatoms chosen from the group of O, S and N wherein S and N may be optionally oxidized;

D^1 to D^4 form an accessible substituted six membered ring, optionally containing up to two nitrogen atoms;

R is at least one substituent chosen from the group of R^7, or Q-C_{1-4}alkyl, Q-C_{2-4}alkenyl, Q-C_{2-4}alkynyl, optionally substituted by one or more of =O, R^{11} or R^7;

R^* is H, Q-C_{1-6}alkyl, Q-C_{1-6}oxoalkyl, Q-C_{2-6}alkenyl, Q-C_{3-4}oxoalkenyl, Q-C_{3-4}oxoalkynyl, Q-C_{2-4}alkynyl, C_{3-6}cycloalkyl, Ar or Het, optionally substituted by one or more of R^{11};

Q is H, C_{3-6}cycloalkyl, Het or Ar;

R^7 is -COR^8, -$COCR'_2R^9$, -$C(S)R^8$, -$S(O)_mOR'$, -$S(O)_mNR'R''$, -PO(OR'), -$PO(OR')_2$, -$B(OR')_2$, -NO_2 and Tet;

R^8 is -OR', -NR'R", -NR'SO_2R', -NR'OR', -$OCR'_2C(O)OR'$, -$OCR'_2OC(O)$-R', -$OCR'_2C(O)NR'_2$, CF_3 or AA;

R^9 is -OR', -CN, -$S(O)_rR'$, $S(O)_mNR'_2$, -C(O)R' C(O)NR'_2 or -CO_2R';

R^{11} is H, halo, -OR^{12}, -CN, -$NR'R^{12}$, -NO_2, -CF_3, $CF_3S(O)_r$-, -CO_2R', -$CONR'_2$, Q-C_{0-6}alkyl-, Q-C_{1-6}oxoalkyl-, Q-C_{2-6}alkenyl-, Q-C_{2-6}alkynyl-, Q-C_{0-6}alkyloxy-, Q-C_{0-6}alkylamino- or Q-C_{0-6}alkyl-$S(O)_r$-;

R^{12} is R', -C(O)R', -$C(O)NR'_2$, -$C(O)OR^{15}$, -$S(O)_mR'$ or $S(O)_mNR'_2$;

R^{13} is R', -CF_3, -SR', or -OR';

R^{14} is R', C(O)R', CN, NO_2, SO_2R' or $C(O)OR^{15}$;

R^{15} is H, C_{1-6}alkyl or Ar-C_{0-4}alkyl;
R' is H, C_{1-6}alkyl, C_{3-7}cycloalkyl-C_{0-4}alkyl or Ar-C_{0-4}alkyl;
R" is R', -C(O)R' or -C(O)OR^{15};
R"' is R" or AA2;
AA1 is an amino acid attached through its amino group and having its carboxyl group optionally protected, and AA2 is an amino acid attached through its carboxyl group, and having its amino group optionally protected;
m is 1 or 2;
n is 0 to 3;
p is 0 or 1; and
t is 0 to 2; or
pharmaceutically acceptable salts thereof.

3. A compound according to claim 2 wherein:
A^1 is $CR^1R^{1'}$, CR^1, NR^1, N, O or $S(O)_x$;
A^2 is $CR^2R^{2'}$, CR^2, NR^2;
A^3 is $CR^3R^{3'}$, CR^3, NR^3, N, O or $S(O)_x$;
A^4 is $CR^4R^{4'}$, CR^4, NR^4, or N;
A^5 is $CR^5R^{5'}$, CR^5, NR^5, N, O or $S(O)_x$;
D^1-D^4 are CH or N;
R^1 and $R^{1'}$ are R^* or R, or together are =O;
R^2 and $R^{2'}$ are R^*, R or =O;
R^3 and $R^{3'}$ are R^*, R or =O;
R^4 and $R^{4'}$ are R^*, R or =O;
R^5 and $R^{5'}$ are R^*, R or =O; and
x is 0, 1 or 2.

4. A compound according to claim 2 wherein:
A^1 is $CR^1R^{1'}$, CR^1, NR^1, N, O or S; A^2 is $CR^2R^{2'}$, NR^2 or CR^2; A^3 is $CR^3R^{3'}$; A^4 is $CR^4R^{4'}$, CR^4, NR^4, or N; A^5 is $CR^5R^{5'}$, CR^5, NR^5, N, O; D^1 and D^4 are CH; D^2 or D^3 is CH^6; R^2 or R^4 are R; R^3,$R^{3'}$ and R^5,$R^{5'}$ are =O or R^*,H.

5. A compound according to claim 2 wherein:
A^1 is CHR^1, CR^1, NR", N or S; A^2 is CR^2 or $CR^2R^{2'}$; A^3 is $CR^3R^{3'}$; A^4 is $CR^4R^{4'}$ or NR^4; A^5 is $CR^5R^{5'}$ D^1- D^4 are CH.

6. A compound according to claim 2 wherein:

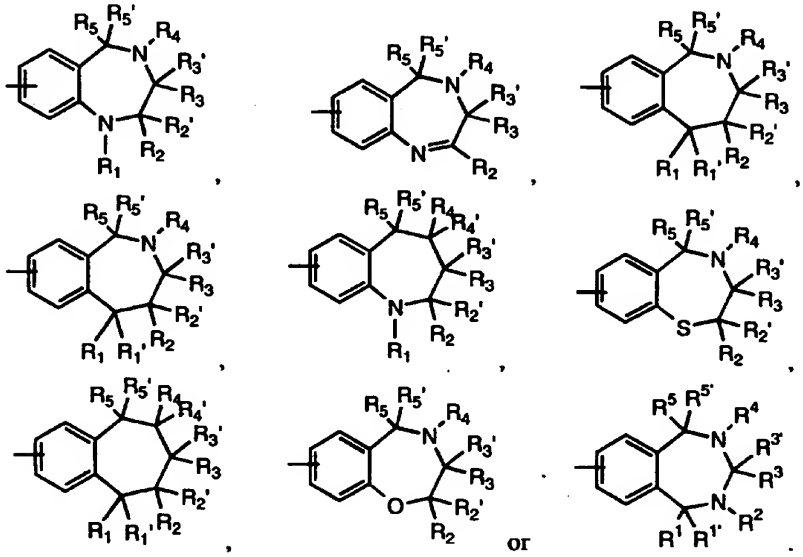
A^1 is CR^1, A^2 is CR^2, A^3 is C=O, A^4 is NR^4 and A^5 are CHR^5.

7. A compound according to claim 2 wherein:
A^1 is NR^1, A^2 is $CHCR^2$, A^3 is $CR^3R^{3'}$, A^4 is NR^4, and A^5 are C=O.

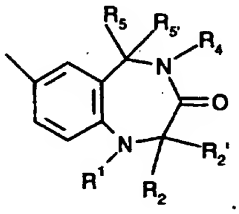
8. A compound according to claim 2 wherein:
A^1 and A^4 are C=O, A^2 is NR^2, A^3 is $CHR^{3'}$ and A^5 is NR^5.

9. A compound according to claim 2 wherein:
A^1 is NR^1, A^2 is CHR^2, A^3 is C=O, A^4 is NR' and A^5 is CHR^5.

10. A compound according to claim 2 wherein:

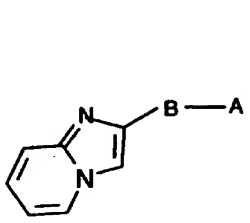


11. A compound according to claim 2 wherein:



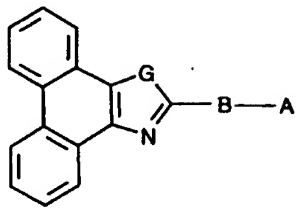
12. A compound according to claim 11 wherein:
R^1 is H or C_{1-4}alkyl; R^2, $R^{2'}$ are H,-CH_2CO_2H; and $R^5R^{5'}$ are H,H.

13. A compound according to formula (XXI) or (XXII):



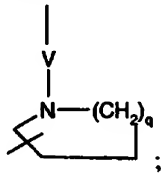
(XXI)

or



(XXII)

wherein:
B is -$(CHR^g)_a$-U- $(CHR^g)_b$-V- or phenyl or



;

A is a fibrinogen receptor antagonist template;
U and V are absent or CO, CR^g_2, $C(=CR^g_2)$, $S(O)_k$, O, NR^g, CR^gOR^g,
$CR^g(OR^k)CR^g_2$, $CR^g_2CR^g(OR^k)$, $C(O)CR^g_2$, $CR^g_2C(O)$, CON R^i N R^i CO
OC(O), C(O)O, C(S)O, OC(S), C(S)NR^g, $NR^gC(S)$, $S(O)_2NR^g$, $NR^gS(O)_2$
N=N, NR^gNR^g, $NR^gCR^g_2$, $NR^gCR^g_2$, CR^g_2O, OCR^g_2, C≡C or CR^g=CR^g;
G is NR^e, S or O;
R^g is H, C_{1-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl or Ar- C_{0-6}alkyl;
R^k is R^g, -C(O)R^g, or -C(O)OR^f;
R^i is is H, C_{1-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl, Ar- C_{0-6}alkyl,
Het-$(CH_2)_{0-6}$-U'-$(CH_2)_{1-6}$-, C_{3-7}cycloalkyl-$(CH_2)_{0-6}$-U'-$(CH_2)_{1-6}$-, or
Ar-$(CH_2)_{0-6}$-U'-$(CH_2)_{1-6}$-or C_{1-6}alkyl substituted by one to three groups
chosen from halogen, CN, NR^g_2, OR^g, SR^g, CO_2R^g, and $CON(R^g)_2$;
R^f is H, C_{1-6}alkyl or Ar-C_{1-6}alkyl;
R^e is H, C_{1-6}alkyl, Ar-C_{1-6}alkyl, Het-C_{1-6}alkyl, C_{3-7}cycloalkyl-C_{1-6}alkyl,
$(CH_2)_qOH$ or $(CH_2)_kCO_2R^g$;

U' is $CONR^f$ or NR^fCO;

k is 0, 1 or 2;

q is 1 or 2;

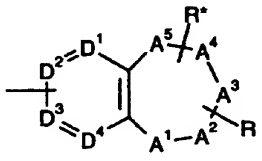
a is 0, 1 or 2;

b is 0, 1 or 2;

R^b and R^c are independently selected from H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, or C_{3-6}cycloalkyl-C_{0-6}alkyl, halogen, CF_3, OR^f, $S(O)_kR^f$, COR^f, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, or R^b and R^c are joined together to form a five or six membered aromatic or non-aromatic carbocyclic or heterocyclic ring, optionally substituted by up to three substituents chosen from halogen, CF_3, C_{1-4}alkyl, OR^f, $S(O)_kR^f$, COR^f, CO_2R^f OH, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, and $CH_2N(R^f)_2$; or methylenedioxy;

or pharmaceutically acceptable salts thereof.

14. A compound according to claim 13 wherein the fibrinogen receptor antagonist template A is



wherein:

A^1 to A^5 form an accessible substituted seven-membered ring, which may be saturated or unsaturated, optionally containing up to two heteroatoms chosen from the group of O, S and N wherein S and N may be optionally oxidized;

D^1 to D^4 form an accessible substituted six membered ring, optionally containing up to two nitrogen atoms;

R is at least one substituent chosen from the group of R^7, or Q-C_{1-4}alkyl, Q-C_{2-4}alkenyl, Q-C_{2-4}alkynyl, optionally substituted by one or more of =O, R^{11} or R^7;

R^* is H, Q-C_{1-6}alkyl, Q-C_{1-6}oxoalkyl, Q-C_{2-6}alkenyl, Q-C_{3-4}oxoalkenyl, Q-C_{3-4}oxoalkynyl, Q-C_{2-4}alkynyl, C_{3-6}cycloalkyl, Ar or Het, optionally substituted by one or more of R^{11};

Q is H, C_{3-6}cycloalkyl, Het or Ar;

R^7 is $-COR^8$, $-COCR'_2R^9$, $-C(S)R^8$, $-S(O)_mOR'$, $-S(O)_mNR'R''$, $-PO(OR')$, $-PO(OR')_2$, $-B(OR')_2$, $-NO_2$ and Tet;

R^8 is -OR', -NR'R", -NR'SO_2R', -NR'OR', -OCR'$_2$C(O)OR', -OCR'$_2$OC(O)-R', -OCR'$_2$C(O)NR'$_2$, CF_3 or AA;

R^9 is -OR', -CN, -S(O)$_r$R', S(O)$_m$NR'$_2$, -C(O)R' C(O)NR'$_2$ or -CO_2R';

R^{11} is H, halo, -OR^{12}, -CN, -NR'R^{12}, -NO_2, -CF_3, CF_3S(O)$_r$-, -CO_2R', -CONR'$_2$, Q-C_{0-6}alkyl-, Q-C_{1-6}oxoalkyl-, Q-C_{2-6}alkenyl-, Q-C_{2-6}alkynyl-, Q-C_{0-6}alkyloxy-, Q-C_{0-6}alkylamino- or Q-C_{0-6}alkyl-S(O)$_r$-;

R^{12} is R', -C(O)R', -C(O)NR'$_2$, -C(O)OR^{15}, -S(O)$_m$R' or S(O)$_m$NR'$_2$;

R^{13} is R', -CF_3, -SR', or -OR';

R^{14} is R', C(O)R', CN, NO_2, SO_2R' or C(O)OR^{15};

R^{15} is H, C_{1-6}alkyl or Ar-C_{0-4}alkyl;

R' is H, C_{1-6}alkyl, C_{3-7}cycloalkyl-C_{0-4}alkyl or Ar-C_{0-4}alkyl;

R" is R', -C(O)R' or -C(O)OR^{15};

R'" is R" or AA2;

AA1 is an amino acid attached through its amino group and having its carboxyl group optionally protected, and AA2 is an amino acid attached through its carboxyl group, and having its amino group optionally protected;

m is 1 or 2;

n is 0 to 3;

p is 0 or 1; and

t is 0 to 2; or

pharmaceutically acceptable salts thereof.

15. A compound according to claim 14 wherein:

A^1 is $CR^1R^{1'}$, CR^1, NR^1, N, O or S(O)$_x$;

A^2 is $CR^2R^{2'}$, CR^2, NR^2;

A^3 is $CR^3R^{3'}$, CR^3, NR^3, N, O or S(O)$_x$;

A^4 is $CR^4R^{4'}$, CR^4, NR^4, or N;

A^5 is $CR^5R^{5'}$, CR^5, NR^5, N, O or S(O)$_x$;

D^1-D^4 are CH or N;

R^1 and $R^{1'}$ are R^* or R, or together are =O;

R^2 and $R^{2'}$ are R^*, R or =O;

R^3 and $R^{3'}$ are R^*, R or =O;

R^4 and $R^{4'}$ are R^*, R or =O;

R^5 and $R^{5'}$ are R^*, R or =O; and

x is 0, 1 or 2.

16. A compound according to claim 14 wherein:

A^1 is $CR^1R^{1'}$, CR^1, NR^1, N, O or S; A^2 is $CR^2R^{2'}$, NR^2 or CR^2; A^3 is $CR^3R^{3'}$; A^4 is $CR^4R^{4'}$, CR^4, NR^4, or N; A^5 is $CR^5R^{5'}$, CR^5, NR^5, N, O; D^1 and D^4 are CH; D^2 or D^3 is CH^6; R^2 or R^4 are R; R^3,$R^{3'}$ and R^5,$R^{5'}$ are =O or R^*,H.

17. A compound according to claim 14 wherein:
A^1 is CHR^1, CR^1, NR", N or S; A^2 is CR^2 or $CR^2R^{2'}$; A^3 is $CR^3R^{3'}$; A^4 is $CR^4R^{4'}$ or NR^4; A^5 is $CR^5R^{5'}$ D^1- D^4 are CH.

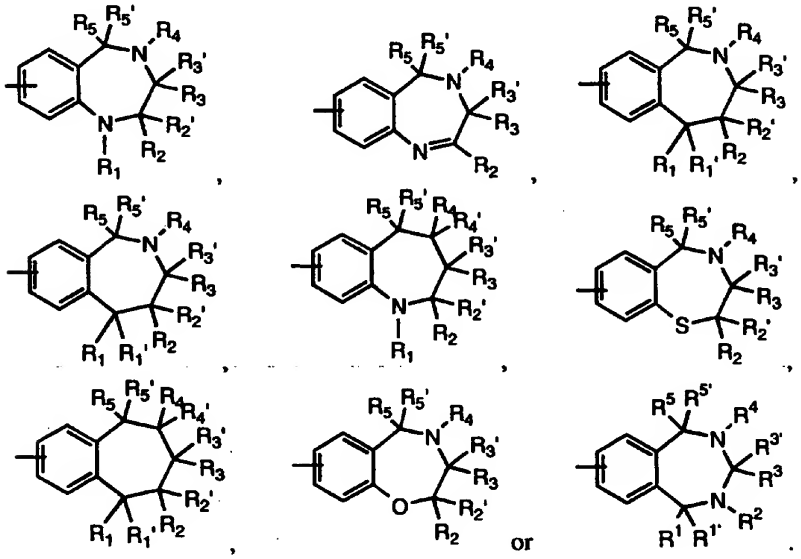
18. A compound according to claim 14 wherein:
A^1 is CR^1, A^2 is CR^2, A^3 is C=O, A^4 is NR^4 and A^5 are CHR^5.

19. A compound according to claim 14 wherein:
A^1 is NR^1, A^2 is $CHCR^2$, A^3 is $CR^3R^{3'}$, A^4 is NR^4, and A^5 are C=O.

20. A compound according to claim 14 wherein:
A^1 and A^4 are C=O, A^2 is NR^2, A^3 is $CHR^{3'}$ and A^5 is NR^5.

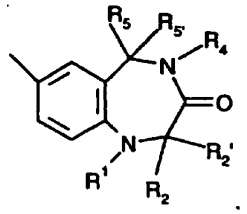
21. A compound according to claim 14 wherein:
A^1 is NR^1, A^2 is CHR^2, A^3 is C=O, A^4 is NR' and A^5 is CHR^5.

22. A compound according to claim 14 wherein:



or

23. A compound according to claim 14 wherein:



24. A compound according to claim 23 wherein:
R^1 is H or C_{1-4}alkyl; R^2, $R^{2'}$ are H,-CH_2CO_2H; and $R^5R^{5'}$ are H,H.

25. A compound selected from the group of:

5-[[[(Benzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-benzimidazole-2-aminoacetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]-methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[(5-trifluoromethylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(4,7-dimethoxybenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(4-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

S)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[N-(benzimidazol-2-yl)methyl-N-(2-cyanomethyl)amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(4-phthalimidobutyl)-1H-1,4-benzodiazepine-2-acetic acid;

4-[[[3-(Benzimidazol-2-yl)propyl]amino]carbonyl]piperidine-1-acetic acid;

4-[[[3-(Benzimidazol-2-yl)propyl]amino]carbonyl]phenylacetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5,7-dimethylbenzimidazol-2-

yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]-carbonyl]-4-[2-(3,4-methylenedioxyphenyl)ethyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]-carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetamide;

(±)-2,3,4,5-Tetrahydro-7-[[[[1-[(benzimidazol-2-yl)methyl]benzimidazol-2-yl]methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[bis[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(4-azabenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-(3,3-dimethylbutyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[2-(benzimidazol-2-yl)acetyl]amino]-5-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(5,6-difluorobenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[bis[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-4-methyl-7-[[[(4-nitrobenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2,2,2-trifluoroethyl)-1H-1,4-benzodiazepine-2-acetic acid;

(±)-4-[4-[[[(1H-Benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-phenylbutanoic acid;

(±)-3-[[[4-(4-Azabenzimidazol-2-yl)butanoyl]glycyl]amino]-4-pentynoic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[[1-(2-hydroxyethyl)benzimidazol-2-yl]methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-(2-methoxyethyl)-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(4-aminobenzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

Ethyl (S)-2,3,4,5-tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate;

(S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid, [(2,2-dimethyl-2-methoxyacetyl)oxy]methyl ester;

2,3,4,5-Tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid;

(±)-N-[2-(Aminomethyl)-4-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]aspartic acid;

(±)-2,3,4,5-Tetrahydro-4-methyl-3-oxo-7-[[[(phenanthrimidazol-2-yl)methyl]amino]carbonyl]-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[3-(benzimidazol-2-yl)phenyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-4-[4-[[[(Benzimidazol-2-yl)methyl]methylamino]carbonyl]phenyl]-3-(dimethylaminocarbonyl)butanoic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-[2-(pyrid-3-yl)ethyl]-1H-1,4-benzodiazepine-2-acetate;

(S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]methylamino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

±)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-[[4-(2-carboxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-2-

hydroxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;

Ethyl (S)-2,3,4,5-tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetate;

2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-[[[(+)-biotinoyl]amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-(2RS)-acetic acid;

2,3,4,5-Tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(imidazo(1,2a)pyrid-2-yl)methyl]methylamino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(S)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-5-[[2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepin-2-yl]methyl]tetrazole;

(S)-2,3,4,5-Tetrahydro-7-[[[(4-aza-5-methylbenzimidazol-2-yl)methyl]amino]carbonyl]-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[3-(benzimidazol-2-yl)propyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-(4-aminobutyl)amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;

(±)-2,3,4,5-Tetrahydro-7-[[[(benzimidazol-2-yl)methyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-(N-hydroxy)acetamide;

Ethyl (±)-3-[[[2-(Benzimidazol-2-yl)ethyl]amino]succinoyl]amino-4-pentynoate;

(±)-3-[[[2-(Benzimidazol-2-yl)ethyl]amino]succinoyl]amino-4-pentynoic acid;

(±)-2,3,4,5-Tetrahydro-7-[[N-[(benzimidazol-2-yl)methyl]-N-[[4-(4-azido-3-iodo-2-hydroxybenzoyl)amino]butyl]amino]carbonyl]-3-oxo-4-(2-phenylethyl)-1H-1,4-benzodiazepine-2-acetic acid;

2,3,4,5-Tetrahydro-7-[[[(1S)-(benzimidazol-2-yl)ethyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid;

2,3,4,5-Tetrahydro-7-[[[(1R)-(benzimidazol-2-yl)ethyl]amino]carbonyl]-4-methyl-3-oxo-1H-1,4-benzodiazepine-(2S)-acetic acid; and

(±)-7-[[[(4,5-Dimethyl-1H-imidazol-2-yl)methyl]methylamino]carbonyl]-2,3,4,5-tetrahydro-4-methyl-3-oxo-1H-1,4-benzodiazepine-2-acetic acid;
or pharmaceutically acceptable salts thereof.

26. A compound selected from the group of:

3-[[3-[2-(benzimidazol-2-yl)ethyl]isoxazolin-5(R,S)-yl]acetyl]amino-3(R,S)-methylpropanoic acid;

3-{3,4-dihydro-8-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]-1-methyl-2,5-dioxo-1H-1,4-benzodiazepine}-4-propanoic acid;

3-{4H-imidazo[1,2-a][1,4]benzodiazepine-5(6H)-1-methyl-6-oxo-9-[[[(benzimidazol-2-yl)methyl]methylamino]carbonyl]}-4-propanoic acid;

4-[4-[2-(1H-benzimidazol-2-yl)ethyl]-1-piperazinyl]-1-piperidineacetic acid;

1-hydroxy-4-[4-[3-(1H-benzimidazol-2-yl)propyl]-1-piperazinyl]-cyclohexaneacetic acid;

N-[3-[1-[[2-(2-Benzimidazolyl)ethyl]carbonyl]piperidinyl]carbonyl]-β-alanine;

2-[(Benzimidazol-2-yl)methyl]- 5-[2-(carboxy-ethyl)amino]carbonyl] -2,3-dihydro-3-oxo-1H-isoindole;

[3(R)-[2-(benzimidazol-2-yl)ethyl]-2-oxopiperidinyl]acetyl-3(R)-methyl -β-alanine;

4-[[[[2-(benzimidazolyl)methyl]carbonyl]methylamino]-acetyl]phenoxyacetic acid;

4-[[[[2-(Benzimidazolyl)methyl]carbonyl]methylamino]acetyl]-1,2-phenylenedioxydiacetic acid;

N-[3-[[[(2-Benzimidazolyl)methyl]carbonyl]amino]benzoyl]-β-alanine;

[[1-[N-[[(2-Benzimidazolyl)methyl]carbonyl]tyrosyl]-4-piperidinyl]oxy]acetic acid;

(S)-4-[[[(2-Benzimidazolyl)methyl]carbonyl]glycyl]-3-methoxycarbonylmethyl-2-oxopiperazine-1-acetic acid;

(3S,5S)-5-[[4-[(2-Benzimidazolyl)methyl]phenyl]oxymethyl]-3-carboxymethyl-2-pyrrolidinone;

1-[(2-Benzimidazolyl)methyl]-3-[4-(2-carboxyethyl)phenyl]-4-methoxy-3-pyrrolin-2-one;

2-[6-(benzimidazol-2-yl) methylaminocarbonyl)-1,2,3,4-tetrahydroisoquinolinyl]acetic acid;

2-[6-(benzimidazol-2-yl)methylaminocarbonyl)-1-oxo-1,2,3,4-tetrahydroisoquinolinyl]acetic acid;

2-[6-((benzimidazol-2-yl)methylcarbonylamino)tetralin]acetic acid;
2-[6-((benzimidazol-2-yl)methylaminocarbonyl)tetralin]acetic acid;
2-[5-((benzimidazol-2-yl)methylcarbonylamino)-benzofuran]-propionic acid;
2-[5-((benzimidazol-2-yl)methylcarbonylamino)-2,3-dihydro-benzofuran]-propionic acid;
2-[5-(6-aminopyridinyl-2-methylaminocarbonyl)-benzofuran]-propionic acid;
2-[5-((benzimidazol-2-yl)methylaminocarbonyl)-2,3-dihydro-benzofuran]-propionic acid; or
1-[(1H-benzimidazol-2-yl)methyl]-3-{4[(2-ethoxycarbonyl)ethyl)]phenyl}-3-oxo-imidazolidine;
or pharmaceutically acceptable salts thereof.

27. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a compound according to any one of claims 1-26.

28. A method of inhibiting a vitronectin receptor in a mammal which comprises administering an effective amount of a compound according to formula (I) or (II) or (III) or (IV) or (V) as defined in claim 1.

29. A method according to claim 28 wherein the compound inhibits the vitronectin receptor with a Ki at the vitronectin receptor that is ten-fold greater than the Ki for said compound at the fibrinogen receptor.

30. A method according to claim 28 wherein the compound inhibits the vitronectin receptor with a Ki at the vitronectin receptor that is thirty-fold greater than the Ki for said compound at the fibrinogen receptor.

31. A method according to claim 28 wherein the compound inhibits the vitronectin receptor with a Ki at the vitronectin receptor that is a hundred-fold greater than the Ki for said compound at the fibrinogen receptor.

32. A method according to claim 28 for treating diseases wherein bone resorption is a factor.

33. A method according to claim 28 for treating osteoporosis, inflammation, restenosis or atherosclerosis.

34. A method of inhibiting a vitronectin receptor in a mammal which comprises administering an effective amount of a compound according to formula (XXI) or (XXII) as defined in claim 13.

35. A method according to claim 34 wherein the compound inhibits the vitronectin receptor with a Ki at the vitronectin receptor that is ten-fold greater than the Ki for said compound at the fibrinogen receptor.

36. A method according to claim 34 wherein the compound inhibits the vitronectin receptor with a Ki at the vitronectin receptor that is thirty-fold greater than the Ki for said compound at the fibrinogen receptor.

37. A method according to claim 34 wherein the compound inhibits the vitronectin receptor with a Ki at the vitronectin receptor that is a hundred-fold greater than the Ki for said compound at the fibrinogen receptor.

38. A method according to claim 34 for treating diseases wherein bone resorption is a factor.

39. A method according to claim 34 for treating osteoporosis, inflammation, restenosis or atherosclerosis.

40. A method of inhibiting a vitronectin receptor in a mammal which comprises administering an effective amount of a compound according to claim 25.

41. A method according to claim 40 wherein the compound inhibits the vitronectin receptor with a Ki at the vitronectin receptor that is ten-fold greater than the Ki for said compound at the fibrinogen receptor.

42. A method according to claim 40 wherein the compound inhibits the vitronectin receptor with a Ki at the vitronectin receptor that is thirty-fold greater than the Ki for said compound at the fibrinogen receptor.

43. A method according to claim 40 wherein the compound inhibits the vitronectin receptor with a Ki at the vitronectin receptor that is a hundred-fold greater than the Ki for said compound at the fibrinogen receptor.

44. A method according to claim 40 for treating diseases wherein bone resorption is a factor.

45. A method according to claim 40 for treating osteoporosis, inflammation, restenosis or atherosclerosis.

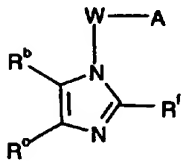
46. The use of a compound according to any one of claims 1-26 in the manufacture of a medicament.

47. The use of a compound according to any one of claims 1-26 in the manufacture of a medicament for the inhibition of the vitronectin receptor in a mammal in need thereof.

48. The use of a compound according to any one of claims 1-26 in the manufacture of a medicament for the treatment of diseases in which bone resorption is a factor.

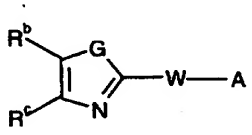
49. The use of a compound according to any one of claims 1-26 in the manufacture of a medicament for the treatment of osteoporosis, inflammation, restenosis, or atherosclerosis.

50. A process for preparing a compound of the formula (I) or (II) or (III) or (IV) or (V):



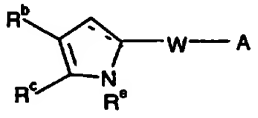
(I)

or



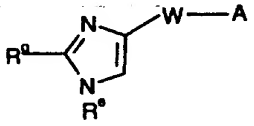
(II)

or



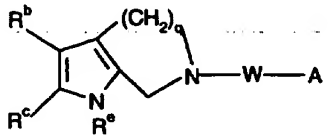
(III)

or



(IV)

or



(V)

wherein:

W is - $(CHR^g)_b$-V'- or phenyl;

A is a fibrinogen receptor antagonist template;
V' is $CONR^{21}$ or $NR^{21}CO$;

G is NR^e, S or O;

R^g is H, C_{1-6}alkyl, Het-C_{0-6}alkyl, C_{3-7}cycloalkyl-C_{0-6}alkyl or Ar- C_{0-6}alkyl;

R^{21} is Het-$(CH_2)_{0-6}$-U'-$(CH_2)_{1-6}$-, C_{3-7}cycloalkyl-$(CH_2)_{0-6}$-U'-$(CH_2)_{1-6}$-, or

Ar-$(CH_2)_{0-6}$-U'-$(CH_2)_{1-6}$-;

U' is $CONR^f$ or NR^fCO;

R^f is H, C_{1-6}alkyl or Ar-C_{1-6}alkyl;

R^e is H, C_{1-6}alkyl, Ar-C_{1-6}alkyl, Het-C_{1-6}alkyl, C_{3-7}cycloalkyl-C_{1-6}alkyl, $(CH_2)_qOH$ or $(CH_2)_kCO_2R^g$;
k is 0, 1 or 2;

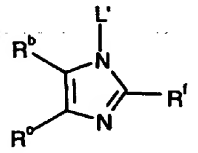
q is 1 or 2;

b is 0, 1 or 2;

R^b and R^c are independently selected from H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, or C_{3-6}cycloalkyl-C_{0-6}alkyl, halogen, CF_3, OR^f, $S(O)_kR^f$, COR^f, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$, or R^b and R^c are joined together to form a five or six membered aromatic or non-aromatic carbocyclic or heterocyclic ring, optionally substituted by up to three substituents chosen from halogen, CF_3, C_{1-4}alkyl, OR^f, $S(O)_kR^f$, COR^f, CO_2R^f OH, NO_2, $N(R^f)_2$, $CO(NR^f)_2$, and $CH_2N(R^f)_2$, or methylenedioxy;

or a pharmaceutically acceptable salt thereof,
which process comprises:

(i) for formula (I) compounds, reacting a compound of the formula (Ia) with a compound of formula (Ib):



(Ia)

L"-A

(Ib)

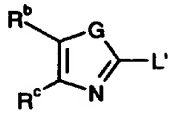
wherein:

R^b, R^c, R^f, and A are as defined in formula (I), with any reactive functional groups protected; and

L' and L" are groups which react to form an amide bond in the moiety W or L' is phenyl substituted by -$SnBu_3$, and L" is halo;

and thereafter removing any protecting groups, and optionally forming a pharmaceutically acceptable salt; or

(ii) for formula (II) compounds, reacting a compound of the formula (IIa) with a compound of the formula (Ib):



(IIa)

L"-A

(Ib)

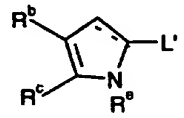
wherein:

R^b, R^c, G and A are as defined in formula (I), with any reactive functional groups protected; and

L' and L" are groups which react to form an amide bond in the moiety W or L' is phenyl substituted by -$SnBu_3$, and L" is halo;

and thereafter removing any protecting groups, and optionally forming a pharmaceutically acceptable salt; or

(iii) for formula (III) compounds, reacting a compound of the formula (IIIa) with a compound of the formula (Ib):



(IIIa)

L"-A

(Ib)

wherein:

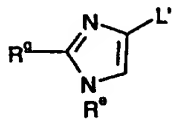
R^b, R^c, R^e, and A are as defined in formula(I), with any reactive functional groups protected; and

L' and L" are groups which react to form an amide bond in the moiety W or

L' is phenyl substituted by -$SnBu_3$, and L" is halo;

and thereafter removing any protecting groups, and optionally forming a pharmaceutically acceptable salt; or

(iv) for formula (IV) compounds, reacting a compound of the formula (IVa) with a compound of the formula (Ib):



(IVa) L"-A (Ib)

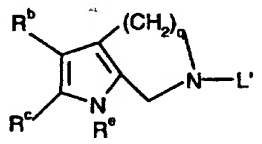
wherein:

R^g, R^e, and A are as defined in formula(I), with any reactive functional groups protected; and

L' and L" are groups which react to form an amide bond in the moiety W or L' is phenyl substituted by -$SnBu_3$, and L" is halo;

and thereafter removing any protecting groups, and optionally forming a pharmaceutically acceptable salt; or

(v) for formula (V) compounds, reacting a compound of the formula (Va) with a compound of the formula (Ib):



(Va) L"-A (Ib)

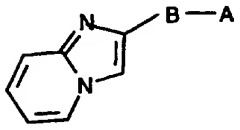
wherein:

R^g, R^e, and A are as defined in formula(I), with any reactive functional groups protected; and

L' and L" are groups which react to form an amide bond in the moiety W or L' is phenyl substituted by -$SnBu_3$, and L" is halo;

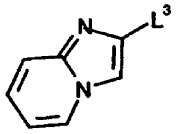
and thereafter removing any protecting groups, and optionally forming a pharmaceutically acceptable salt.

51. A process for preparing a compound of the formula (XXI):



(XXI)

wherein A and B are as defined in claim 13,
which process comprises reacting a compound of the formula (XXV) with a compound of the formula (XXVI):



L^4-A

(XXV) (XXVI)

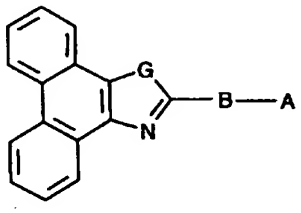
wherein:

A is as defined in claim 13, with any reactive functional groups protected; and

L^3 and L^4 are groups which react to form a covalent bond in the moiety B;

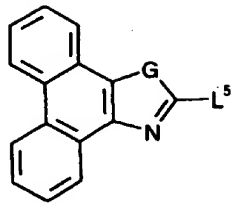
and thereafter removing any protecting groups, and optionally forming a pharmaceutically acceptable salt.

52. A process for preparing a compound of the formula (XXI):



(XXII)

wherein A, B and G are as defined in claim 13,
which process comprises reacting a compound of the formula (XXVII) with a compound of the formula (XXVIII):



(XXVII)

L^6-A

(XXVIII)

wherein:

A and G are as defined herinabove, with any reactive functional groups protected; and

L^5 and L^6 are groups which react to form a covalent bond in the moiety B; and thereafter removing any protecting groups, and optionally forming a pharmaceutically acceptable salt.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/20748

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :Please See Extra Sheet.
US CL :514/221; 540/513
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/221; 540/513

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3,627,754 A (NING ET AL.) 14 December 1971(14.12.71), see entire document, especially column 1.	1-52, parts

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 04 MARCH 1997	Date of mailing of the international search report 21 MAR 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer ROBERT W. RAMSUER Telephone No. (703) 308-1231

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/20748

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-52, parts
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/20748

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 31/40; CO7D 487/04

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE
2. Where no meaningful search could be carried out, specifically:

The multitude of variables and their permutations and combinations (e.g. W,A V', G Ra, the provisos, the formulae, etc.) result in claimed subject matter that is so broad in scope that it is rendered virtually incomprehensible and thus no meaningful search can be given. Note also that the claimed subject matter lacks a significant structural element qualifying as the special technical feature that clearly defines a contribution over the art. The subject matter claimed does not contain a single technical feature as note the many fomulae (e.g. I, II, III, etc.). Therefore, the first discernable invention as found in Example 1, the compound therein, the pharmaceutical composition therewith, the method of preparation thereof and the method of treating osteoporosis therewith has been searched.